EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	341	iopanoic and albumin	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:02
L2	314	iopanoic and albumin and contrast	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:02
L3	31	iopanoic and albumin.ab. and contrast	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:15
L4	0	iopanoic.ab. and albumin.ab. and contrast	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:02
L5	0	iopanoic.ab. and albumin.ab. and contrast.ab.	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:03
L6	0	(Gd-1B4M) and albumin.ab. and contrast	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:16
L7	6	Gd-1B4M	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 11:48
L8	4	l7 and albumin	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 10:19
L9	852	iopamidol	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 11:35
L10	1	l1 and l8	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 11:35
L11	30	l1 and l9	US-PGPUB; USPAT; DERWENT	ADJ	ON	2007/04/06 11:35
L12	0	interstitual infusion	US-PGPUB; USPAT; EPO; DERWENT	ADJ	ON	2007/04/06 11:49
L13	52	interstitial infusion	US-PGPUB; USPAT; EPO; DERWENT	ADJ	ON	2007/04/06 12:15
L14	17	(interstitial infusion) and (image or topography)	US-PGPUB; USPAT; EPO; DERWENT	ADJ	ON	2007/04/06 12:16

10/528310

1° = 9-24-2007

File 5:Biosis Previews(R) 1926-2007/Apr W1

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*File 5: BIOSIS has been enhanced with archival data. Please see HELP NEWS 5 for information.

Set	Items	Description
S1	81	INTERSTITIAL()INFUSION
S2	7	S1 AND IMAG?
S3	36282	(DRUG OR THERAP?) AND (IMAGE OR (X()RAY))
S4	2	S3 AND S1
S5	29636	(DRUF OR THERAP?) AND (MAGNETIC)
S6	5385	(DRUG OR THERAP) AND (MAGNETIC OR (X()RAY)) AND ADMINIST?
S7	6027	(DRUG OR THERAPEUTIC) AND (MAGNETIC OR (X()RAY)) AND ADMINIST?
S8	94	S7 AND INTERSTITIAL
S9	16	THERAPEUTIC AND MAGNETIC AND ADMINIST? AND INTERSTITIAL
S10	10	S8 AND GADOLINIUM
S11	0	ALBUMIN(2W)CONJUGAT?(2W)GADOLINIUM
S12	168	ALBUMIN AND GADOLINIUM
S13	9	S12 AND INTERSTITIAL
S14	0	GS()1B4M
S15	0	GD()1B4M
S16	14	1B4M AND MAGNETIC
S17	9	GADOLINIUM AND 1B4M
S18	0	S17 AND INTERSTITIAL
S19	397	(X()RAY) AND CONTRAST AND THERAPEUTIC
S20	7	S19 AND INTERSTITIAL

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2/7/1

DIALOG(R)File 5:Biosis Previews(R)

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17329851 BIOSIS NO.: 200300287526

A computational model of direct %%%interstitial%%% %%%infusion%%% of macromolecules into the spinal cord.

AUTHOR: Samtinoranont Malisa (Reprint); Banerjee Rupak K; Lonser Russell R

; Morrison Paul F
AUTHOR ADDRESS: Drug Delivery and Kinetics Resource, Division of Bioengineering and Physical Science ORS, 9000 Rockville Pike, Building 13, Room 3N17, Bethesda, MD, 20892, USA**USA
AUTHOR E-MAIL ADDRESS: samtinm@mail.nih.gov
JOURNAL: Annals of Biomedical Engineering 31 (4): p448-461 April 2003 2003
MEDIUM: print
ISSN: 0090-6964 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Convection-enhanced %%%interstitial%%% %%%infusion%%% can deliver macromolecular drugs to large tissue volumes of the central nervous system. To characterize infusion into the spinal cord, an %%%image%%% -based three-dimensional finite element model of the rat spinal cord was developed. The model incorporated convection and diffusion through white and gray matter, including anisotropic transport due to alignment of white matter tracts. Spatial and temporal distribution of the marker substance albumin within the interstitial space was determined. Consistent with previous experiments, predicted distribution was highly anisotropic. Infusing into the dorsal column, albumin was primarily confined to white matter with limited penetration into adjacent gray matter. Distribution was determined primarily by the ratio of fiber-parallel to fiber-perpendicular hydraulic conductivity tensor components (kwm-z/kwm-x), the ratio of transverse white and gray matter hydraulic conductivity (kwm-x/kgm), and tissue porosity. Fits to previous experimental measures of axial and transverse spread, distribution volume, and protein recovery yielded an optimum kwm-z/kwm-x of approximately 20 at 0.1 mul/min. kwm-x/kgm of 100 was sufficient to match experimental transverse distribution data. Best fits to data at 0.1 mul/min were achieved by porosities characteristic of moderate edema (e.g., 0.26). Distribution also varied with catheter placement with more medial placement resulting in greater distribution volumes.

17254769 BIOSIS NO.: 200300213488

Renal medullary %%%interstitial%%% %%%infusion%%% is a flawed technique for examining vasodilator mechanisms in anesthetized rabbits.

AUTHOR: Kalyan Aparna; Eppel Gabriela A; Anderson Warwick P; Oliver Jeremy J; Evans Roger G
AUTHOR E-MAIL ADDRESS: roger.evans@med.monash.edu.au

JOURNAL: Journal of Pharmacological and Toxicological Methods 47 (3): p 153-159 May-June 2002 2002
MEDIUM: print
ISSN: 1056-8719 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: In rats, medullary interstitial (MI) infusion is a useful technique for selective delivery of pharmacological agents to the renal medulla, in both acute and chronic experimental settings. We examined the feasibility of using this technique for delivery of vasodilators in rabbits, since this larger species would provide a number of advantages, particularly in long-term studies of circulatory control. Methods: Rabbits were anesthetized with pentobarbitone and artificially ventilated. Catheters were placed in a side branch of the renal artery and/or the renal medullary interstitium. Renal blood flow (RBF) was determined by transit-time ultrasound flowmetry, and blood flow in the cortex and medulla was estimated by laser Doppler flowmetry. Results: Pilot studies showed that renal arterial (IRA) infusions of bradykinin (10-300 ng/kg/min) and adenosine (1-10 ng/kg/min) produced only transient renal vasodilatation. IRA infusions of methylamine hexamethylene methylamine (MAHMA) NONOate (100-1000 ng/kg/min) and acetylcholine (10-250 ng/kg/min) produced dose-dependent and sustained increases in RBF and reductions in arterial pressure at the highest doses. However, IMI infusion of the same doses did not consistently increase medullary laser Doppler flux (MLDF). After IRA MAHMA NONOate and IMI acetylcholine, RBF fell to below its resting level. IRA boluses of acetylcholine (10-1250

ng/kg), bradykinin (2-250 ng/kg), and MAHMA NONOate (100-3000 ng/kg) dose-dependently increased RBF and CLDF and MLDF. Discussion: We had previously validated the IMI infusion technique for intramedullary delivery of vasoconstrictors in rabbits. Our present results indicate that this technique has limited application for delivery of vasodilator agents, in part because counterregulatory vasoconstrictor mechanisms are activated.

2/7/3

16180615 BIOSIS NO.: 200100352454

Saline-enhanced radiofrequency ablation of breast tissue: An in vitro feasibility study

AUTHOR: Boehm Thomas (Reprint); Hilger Ingrid; Mueller Wolfgang; Reichenbach Juergen R; Fleck Marlies; Kaiser Werner A
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JOURNAL: Investigative Radiology 35 (3): p149-157 March, 2000 2000
MEDIUM: print
ISSN: 0020-9996
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: RATIONALE AND OBJECTIVES. The feasibility of radiofrequency (RF) ablation for the treatment of breast tumors was investigated in vitro. The best parameters for ablation of breast tissue were chosen. METHODS. Saline-enhanced RF ablation was performed in human breast tissue specimens and cow udder tissue. Temperature profiles were measured depending on RF power (20, 28, 36 W) and NaCl infusion rate (15, 30, 60 mL/h) using eight thermocouples. Lesion development was monitored by ultrasound. Thermolysis efficiency was measured by tissue weight determinations before and after ablation. RESULTS. After RF ablation of

tissue samples, 73.6% turned into a fat/saline emulsion. Ultrasound monitoring showed a cone-shaped hyperechoic area during the first 2 minutes of RF ablation, followed by an irregular expansion of the area. Time-dependent spatial temperature curves were more homogeneous at low infusion rates (15 mL/h). Peak temperatures up to 160degree C were measured. CONCLUSIONS. Controlled RF ablation of breast tissue is feasible. The irregular expansion of RF lesions in fatty breast tissue is due to liquefied fat. Low saline %%%interstitial%%% %%%infusion%%% rates result in better control of lesioning.

2/7/4

14155474 BIOSIS NO.: 199799789534

Chronic %%%interstitial%%% %%%infusion%%% of protein to primate brain: Determination of drug distribution and clearance with single photon emission computerized tomography %%%imaging%%%

AUTHOR: Laske Douglas W; Morrison Paul F; Lieberman Daniel M; Corthesy Mark E; Reynolds James C; Stewart-Henney Patricia A; Koong Sung-Soo; Cummins Alex; Paik Chang H; Oldfield Edward H (Reprint)

AUTHOR ADDRESS: Surgical Neurol. Branch, Natl. Inst. Neurological Disorders and Stroke, Build. 10, Room 5D37, Natl. Inst. Health, Bethesda, MD 20892, USA**USA

JOURNAL: Journal of Neurosurgery 87 (4): p586-594 1997 1997

ISSN: 0022-3085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: High-flow %%%interstitial%%% %%%infusion%%% into the brain, which uses bulk fluid flow to achieve a relatively homogeneous drug distribution in the extracellular space of the brain, has the potential to perfuse large volumes of brain. The authors report reproducible long-term delivery of 111In-diethylenetriamine pentaacetic acid-apotransferrin (111In-DTPA-Tf) (molecular mass 81 kD) to Macaca

mulatta brain and monitoring with single-photon emission computerized tomography (SPECT). The 111In-DTPA-Tf was infused at 1.9 mu-l/minute over 87 hours into the frontal portion of the centrum semiovale using a telemetry-controlled, fully implanted pump. On Days 1, 3, 4, 8, 11, and 15 after beginning the infusion, planar and SPECT scans of 111In-DTPA-Tf were obtained. Spread of protein in the brain ranged from 2 to 3 cm and infusion volumes ranged from 3.9 to 6.7 cm-3. Perfusion of over one-third of the white matter of the infused hemisphere was achieved. From brain SPECT %%%images%%% of 99mTc-hexamethylpropyleneamine oxime, which was administered intravenously before each 111In scan, the authors also found that blood perfusion in the infused region was reduced by less than 5% relative to corresponding noninfused regions. Histological examination at 30 days revealed only mild gliosis limited to the area immediately surrounding the needle tract. These findings indicate that long-term interstitial brain infusion is effective for the delivery of drugs on a multicentimeter scale in the primate brain. The results also indicate that it should be possible to perfuse targeted regions of the brain for extended intervals to investigate the potential utility of neurotrophic factors, antitumor agents, and other materials for the treatment of central nervous system disorders.

2/7/5

DIALOG(R)File 5:Biosis Previews(R)

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13311483 BIOSIS NO.: 199698779316

Increasing volume of distribution to the brain with %%%interstitial%%% %%%infusion%%%: Dose, rather than convection, might be the most important factor

AUTHOR: Kroll Robert A; Pagel Michael A; Muldoon Leslie L; Roman-Goldstein Simon; Neuwelt Edward A (Reprint)

AUTHOR ADDRESS: Dep. Neurol., Oregon Health Sci. Univ., 3181 SW Sam Jackson Park Rd., Portland, OR 97201-3098, USA**USA

JOURNAL: Neurosurgery (Baltimore) 38 (4): p746-754 1996 1996

ISSN: 0148-396X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The volume of distribution in tissue (V-t) that can be achieved by direct %%%interstitial%%% %%%infusion%%% of therapeutic agents into brain is limited. The maintenance of a pressure gradient during %%%interstitial%%% %%%infusion%%% to establish fluid convection has been shown to increase the V-t of small, medium, and large molecules. We have used monocrystalline iron oxide nanocompounds, superparamagnetic particles of sizes the same order of magnitude as virions, to investigate the effect of dose, the volume of infusate, and the time of infusion on the distribution of large molecules in rodent brain. Our initial study in rats (n = 6) replicated the results of a previously described report of convection-enhanced delivery in cats. At a constant rate and concentration, the V-t increased in a linear fashion, proportional to the increases in time, volume, and dose. When using a constant rate and a constant concentration, however, it is unclear which variable or variables (dose, volume, infusion time) have the greatest influence on this effect. Therefore, we assessed each variable independently (n = 12). When the iron dose was increased from 5.3 to 26.5 mu-g, there was a three- to fivefold increase in the V-t, depending on the volume and time of infusion (2 mu-l/20 min, 24 mu-l/20 min, or 24 mu-l/120 min) (P lt 0.001). When the volume of infusate was increased from 2 to 24 mu-l, at an infusion time of 20 minutes and a dose of either 5.3 or 26.5 mu-g, there was a 43 or 52% decline in the V-t, respectively (P = 0.018). When the time for the infusion of 24 mu-l was increased from 20 to 120 minutes, there was a 79% increase in the V-t at a dose of 26.5 mu-g but no change in the V-t at a dose of 5.3 mu-g. The effect associated with infusion time was not significant (P = 0.113). Magnetic resonance %%%imaging%%% was performed to document the distribution of monocrystalline iron oxide nanocompounds in vivo, and histochemical staining for iron was used to document the distribution of monocrystalline iron oxide nanocompounds in tissue sections. The V-t for both methods was calculated by computer %%%image%%% analysis, and the correlation between magnetic resonance and histological volumes was determined (r-2 = 0.93). On the basis of this model, we suggest that dose, rather than convection, might be the most important variable in

maximizing the V-t and improved distribution might be achieved by administering an increased concentration of agent.

2/7/6

12865907 BIOSIS NO.: 199598333740

Convection-enhanced distribution of large molecules in gray matter during interstitial drug infusion

AUTHOR: Liberman Daniel M; Laske Douglas W; Morrison Paul F; Bankiewicz Krzysztof S; Oldfield Edward H (Reprint)

AUTHOR ADDRESS: Build. 10, Room 5D37, Surg. Neurol. Branch, NINDS, Natl. Inst. Health, Bethesda, MD 20892, USA**USA

JOURNAL: Journal of Neurosurgery 82 (6): p1021-1029 1995 1995

ISSN: 0022-3085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Many novel experimental therapeutic agents, such as neurotrophic factors, enzymes, biological modifiers, and genetic vectors, do not readily cross the blood-brain barrier. An effective strategy to deliver these compounds to the central nervous system is required for their application in vivo. Under normal physiological conditions, brain interstitial fluid moves by both bulk flow (convection) and diffusion. It has recently been shown that %%%interstitial%%% %%%infusion%%% into the white matter can be used to increase bulk flow, produce interstitial convection, and efficiently and homogeneously deliver drugs to large regions of brain without significant functional or structural damage. In theory, even more uniform distribution is likely in gray matter. In the current study, four experiments were performed to examine if convection-enhanced delivery could be used to achieve regional distribution of large molecules in gray matter. First, the volume and consistency of anatomical distribution of 20 mu-l of phaseolus vulgaris-leukoagglutinin (PHA-L; molecular weight (MW) 126 kD) after

continuous high-flow microinfusion into the striatum of five rats over 200 minutes were determined using immunocytochemistry and quantified with %%%image%%% analysis. Second, the concentration profile of 14C-albumin (MW 69 kD) infused under identical conditions was determined in four hemispheres using quantitative autoradiography. Third, the volume of distribution after convection-enhanced infusion of 250 or 500 mu-l biotinylated dextran (b-dextran, MW 10 kD), delivered over 310 minutes into the caudate and putamen of a rhesus monkey from one (250 mu-l) or two (500 mu-l) cannulas, was determined using immunocytochemistry and quantified with %%%image%%% analysis. Finally, the ability to target all dopaminergic neurons of the nigrostriatal tract via perfusion of the striatum with subsequent retrograde transport was assessed in three experiments by immunohistochemical analysis of the mesencephalon following a 300-minute infusion of 27 mu-l horseradish peroxidase-labeled wheat germ agglutinin (WGA-HRP) into the striatum. Convection-enhanced delivery reproducibly distributed the large-compound PHA-L throughout the rat striatum (the percent volume of the striatum perfused, V-s, was 86% + 5%; mean + standard deviation) and produced a homogeneous tissue concentration in the perfused region (concentration of 14C-albumin relative to infusate concentration 30% + 5%). In the monkey, the infusion widely distributed b-dextran within the striatum using one cannula (caudate and putamen V-s = 76% and 76%) or two cannulas (V-s = 90% and 71%). Perfusion of the rat striatum with WGA-HRP effectively targeted neurons throughout the pars compacta of the substantia nigra via their efferent connections in the nigrostriatal pathway.
Convection-enhanced infusion into gray matter distributes large molecules extensively at a relatively homogeneous concentration. This technique for effective acute delivery of large molecules into the gray matter has several advantages over diffusion alone and has a wide spectrum of potential applications in laboratory and clinical neuroscience.

12693411 BIOSIS NO.: 199598161244

Chronic %%%interstitial%%% %%%infusion%%% with implanted pumps in primates: SPECT %%%imaging%%% determination of brain drug distribution and clearance

AUTHOR: Laske Dougals W (Reprint); Lieberman Daniel M; Morrison Paul F; Corthesey Marc E; Reynolds James C; Stewart Patricia A; Paik Chang; Oldfield Edward H

AUTHOR ADDRESS: Bethesda, MD, USA**USA

JOURNAL: Journal of Neurosurgery 82 (2): p365A 1995 1995

CONFERENCE/MEETING: Annual Meeting of the American Association of Neurological Surgeons April 22-27, 1995; 19950422

ISSN: 0022-3085

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

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4/7/1

DIALOG(R)File 5:Biosis Previews(R)

13311483 BIOSIS NO.: 199698779316

Increasing volume of distribution to the brain with %%%interstitial%%% %%%infusion%%%: Dose, rather than convection, might be the most important factor

AUTHOR: Kroll Robert A; Pagel Michael A; Muldoon Leslie L; Roman-Goldstein Simon; Neuwelt Edward A (Reprint)

AUTHOR ADDRESS: Dep. Neurol., Oregon Health Sci. Univ., 3181 SW Sam Jackson Park Rd., Portland, OR 97201-3098, USA**USA

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ISSN: 0148-396X

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The volume of distribution in tissue (V-t) that can be achieved by direct %%%interstitial%%% %%%infusion%%% of %%%therapeutic%%% agents

into brain is limited. The maintenance of a pressure gradient during %%%interstitial%%% %%%infusion%%% to establish fluid convection has been shown to increase the V-t of small, medium, and large molecules. We have used monocrystalline iron oxide nanocompounds, superparamagnetic particles of sizes the same order of magnitude as virions, to investigate the effect of dose, the volume of infusate, and the time of infusion on the distribution of large molecules in rodent brain. Our initial study in rats (n = 6) replicated the results of a previously described report of convection-enhanced delivery in cats. At a constant rate and concentration, the V-t increased in a linear fashion, proportional to the increases in time, volume, and dose. When using a constant rate and a constant concentration, however, it is unclear which variable or variables (dose, volume, infusion time) have the greatest influence on this effect. Therefore, we assessed each variable independently (n = 12). When the iron dose was increased from 5.3 to 26.5 mu-g, there was a three- to fivefold increase in the V-t, depending on the volume and time of infusion (2 mu-l/20 min, 24 mu-l/20 min, or 24 mu-l/120 min) (P lt 0.001). When the volume of infusate was increased from 2 to 24 mu-l, at an infusion time of 20 minutes and a dose of either 5.3 or 26.5 mu-g, there was a 43 or 52% decline in the V-t, respectively (P = 0.018). When the time for the infusion of 24 mu-l was increased from 20 to 120 minutes, there was a 79% increase in the V-t at a dose of 26.5 mu-g but no change in the V-t at a dose of 5.3 mu-g. The effect associated with infusion time was not significant (P = 0.113). Magnetic resonance imaging was performed to document the distribution of monocrystalline iron oxide nanocompounds in vivo, and histochemical staining for iron was used to document the distribution of monocrystalline iron oxide nanocompounds in tissue sections. The V-t for both methods was calculated by computer %%%image%%% analysis, and the correlation between magnetic resonance and histological volumes was determined (r-2 = 0.93). On the basis of this model, we suggest that dose, rather than convection, might be the most important variable in maximizing the V-t and improved distribution might be achieved by administering an increased concentration of agent.

12865907 BIOSIS NO.: 199598333740

Convection-enhanced distribution of large molecules in gray matter during interstitial %%%drug%%% infusion

AUTHOR: Liberman Daniel M; Laske Douglas W; Morrison Paul F; Bankiewicz Krzysztof S; Oldfield Edward H (Reprint)

AUTHOR ADDRESS: Build. 10, Room 5D37, Surg. Neurol. Branch, NINDS, Natl. Inst. Health, Bethesda, MD 20892, USA**USA

JOURNAL: Journal of Neurosurgery 82 (6): p1021-1029 1995 1995

ISSN: 0022-3085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Many novel experimental %%%therapeutic%%% agents, such as neurotrophic factors, enzymes, biological modifiers, and genetic vectors, do not readily cross the blood-brain barrier. An effective strategy to deliver these compounds to the central nervous system is required for their application in vivo. Under normal physiological conditions, brain interstitial fluid moves by both bulk flow (convection) and diffusion. It has recently been shown that %%%interstitial%%% %%%infusion%%% into the white matter can be used to increase bulk flow, produce interstitial convection, and efficiently and homogeneously deliver drugs to large regions of brain without significant functional or structural damage. In theory, even more uniform distribution is likely in gray matter. In the current study, four experiments were performed to examine if convection-enhanced delivery could be used to achieve regional distribution of large molecules in gray matter. First, the volume and consistency of anatomical distribution of 20 mu-l of phaseolus vulgaris-leukoagglutinin (PHA-L; molecular weight (MW) 126 kD) after continuous high-flow microinfusion into the striatum of five rats over 200 minutes were determined using immunocytochemistry and quantified with %%%image%%% analysis. Second, the concentration profile of 14C-albumin (MW 69 kD) infused under identical conditions was determined in four hemispheres using quantitative autoradiography. Third, the volume of distribution after convection-enhanced infusion of 250 or 500 mu-l

biotinylated dextran (b-dextran, MW 10 kD), delivered over 310 minutes into the caudate and putamen of a rhesus monkey from one (250 mu-l) or two (500 mu-l) cannulas, was determined using immunocytochemistry and quantified with %%%image%%% analysis. Finally, the ability to target all dopaminergic neurons of the nigrostriatal tract via perfusion of the striatum with subsequent retrograde transport was assessed in three experiments by immunohistochemical analysis of the mesencephalon following a 300-minute infusion of 27 mu-l horseradish peroxidase-labeled wheat germ agglutinin (WGA-HRP) into the striatum. Convection-enhanced delivery reproducibly distributed the large-compound PHA-L throughout the rat striatum (the percent volume of the striatum perfused, V-s, was 86% + 5%; mean + standard deviation) and produced a homogeneous tissue concentration in the perfused region (concentration of 14C-albumin relative to infusate concentration 30% + 5%). In the monkey, the infusion widely distributed b-dextran within the striatum using one cannula (caudate and putamen V-s = 76% and 76%) or two cannulas (V-s = 90% and 71%). Perfusion of the rat striatum with WGA-HRP effectively targeted neurons throughout the pars compacta of the substantia nigra via their efferent connections in the nigrostriatal pathway.
Convection-enhanced infusion into gray matter distributes large molecules extensively at a relatively homogeneous concentration. This technique for effective acute delivery of large molecules into the gray matter has several advantages over diffusion alone and has a wide spectrum of potential applications in laboratory and clinical neuroscience.

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9/7/1

DIALOG(R)File 5:Biosis Previews(R)

19314289 BIOSIS NO.: 200600659684

Chemodosimetry of in vivo tumor liposomal drug concentration using MRI

AUTHOR: Viglianti Benjamin L; Ponce Ana M; Michelich Charles R; Yu Daohai; Abraham Sheela A; Sanders Linda; Yarmolenko Pavel S; Schroeder Thies; MacFall James R; Barboriak Daniel P; Colvin O Michael; Bally Marcel B; Dewhirst Mark W (Reprint)

AUTHOR ADDRESS: Duke Univ, Med Ctr, Dept Radiat Oncol, MSRB 201,Box 3455, Durham, NC 27710 USA**USA
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JOURNAL: Magnetic Resonance in Medicine 56 (5): p1011-1018 NOV 2006 2006
ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Effective cancer chemotherapy depends on the delivery of %%%therapeutic%%% drugs to cancer cells at cytotoxic concentrations. However, physiologic barriers, such as variable vessel permeability, high %%%interstitial%%% fluid pressure, and heterogeneous perfusion, make it difficult to achieve that goal. Efforts to improve drug delivery have been limited by the lack of noninvasive tools to evaluate intratumoral drug concentration and distribution. Here we demonstrate that tumor drug concentration can be measured in vivo using T-1-weighted MRI, following systemic %%%administration%%% of liposomes containing both drug (doxorubicin (DOX)) and contrast agent (manganese (Mn)). Mn and DOX concentrations were calculated using T-1 relaxation times and Mn:DOX loading ratios, as previously described. Two independent validations by high-performance liquid chromatography (HPLC) and histologic fluorescence in a rat fibrosarcoma (FSA) model indicate a concordant linear relationship between DOX concentrations determined using T-1 and those measured invasively. This method of imaging exhibits potential for real-time evaluation of chemotherapeutic protocols and prediction of tumor response on an individual patient basis.

9/7/2

18886592 BIOSIS NO.: 200600231987
Effects of the tumor vasculature targeting agent NGR-TNF on the tumor microenvironment in murine lymphomas
AUTHOR: van Laarhoven H W M (Reprint); Gambarota G; Heerschap A; Lok J;

Verhagen I; Corti A; Toma S; Stampino C; Gallo; van der Kogel A; Punt C J A
AUTHOR ADDRESS: Univ Med Ctr Nijmegen, Dept Med Oncol, POB 9101, NL-6500 HB Nijmegen, Netherlands**Netherlands
AUTHOR E-MAIL ADDRESS: h.vanlaarhoven@onco.umcn.nl
JOURNAL: Investigational New Drugs 24 (1): p27-36 JAN 2006 2006
ISSN: 0167-6997
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: TNF-alpha may improve drug delivery to tumors by alteration of vascular permeability. However, toxicity precludes its systemic %%%administration%%% in patients. NGR-TNF comprises TNF coupled to the peptide CNGRC, which is a ligand for CD 13. CD 13 is expressed on tumor vasculature. Therefore, to assess the efficacy of NGR-TNF its biological effect on tumor vasculature should be measured rather than its effect on tumor growth. The aim of this study was to assess the effects of a low dose of NGR-TNF (5 ng/kg) on vascular permeability, tumor hypoxia, perfusion and proliferation in lymphoma hearing mice. MRI measurements with blood pool contrast agent showed an increased leakage of the contrast agent from the vasculature in NGR-TNF treated tumors compared with controls ($p < 0.05$), Suggesting NGR-TNF-induced vascular permeability. Immunohistochemical analysis two hours after NGR-TNF treatment showed a decrease in tumor hypoxia ($p < 0.1$) and an increase in labeling index of the S-phase marker bromodeoxyuridine ($p < 0.1$), possibly due to an increase in tumor blood flow after NGR-TNF treatment. Although a decrease in tumor hypoxia and an increase in labeling index could have lead to increased tumor growth, in this experiment after one day a decrease in tumor volume was measured. Possibly, the effects on tumor hypoxia and proliferation two hours after treatment are transient and overruled by other, more longlasting effects. For example, the observed increase in vascular permeability may lead to haemoconcentration and increased %%%interstitial%%% pressure, ultimately resulting in an reduction Of tumor blood flow and thus a decrease in tumor growth. A beneficial effect of NGR-TNF in combination with other therapeutical agents may therefore critically depend on the sequence and timing of the

regimens. Currently, NGR-TNF is being tested in clinical studies.

9/7/3

DIALOG(R)File 5:Biosis Previews(R)

18594274 BIOSIS NO.: 200510288774

Liver metastases in rats: Chemoembolization combined with %%%interstitial%%% laser ablation for treatment

AUTHOR: Maataoui Adel (Reprint); Qian Jun; Mack Martin G; Khan Mohammad F; Oppermann Elsie; Roozru Mehry; Schmidt Sabine; Bechstein Wolf O; Vogl Thomas J

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JOURNAL: Radiology 237 (2): p479-484 NOV 2005 2005

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: PURPOSE: To assess the effects of transcatheter arterial chemoembolization (TACE) combined with laser-induced thermotherapy (LITT) for treatment of liver metastases in an animal model.MATERIALS AND METHODS: All experiments were approved by the German government and the institutional animal research review board. After subcapsular liver implantation of colorectal cancer cells in 30 WAG rats (on day 0), the animals group A, TACE was performed. Fourteen days after cancer cells implantation and within 20 minutes after laparotomy and retrograde placement of a microcatheter into the gastroduodenal artery, these rats were injected with mitomycin (0.1 mg), iodized oil (0.1 mL), and degradable starch microspheres (5.0 mg). In the 10 rats in group B, LITT was performed. Also on day 14, the tumors in these animals were exposed to Nd:YAG laser light of 1064 nm at 2 W for 5 minutes. In the 10 rats in group C, combined treatment was %%%administered%%%. TACE was performed on day 14, and LITT was performed on day 21. Tumor volumes were measured

before (on day 13) and after (on day 28) treatment with %%%magnetic%%% resonance (MR) imaging, and the mean tumor growth ratio (day 13 tumor volume divided by day 28 tumor volume) was calculated.RESULTS: The mean tumor volumes measured before and after the treatments were, respectively, 0.11 and 0.60 cm(3) in group A, 0.11 and 0.68 cm(3) in group B, and 0.11 and 0.35 cm(3) in group C. The mean tumor growth ratio was 5.42 in group A, 6.14 in group B, and 3.15 in group C. According to Bonferroni test results, compared with the rats in groups A and B (controls), the group C rats had significantly inhibited tumor growth (P < .01 for both comparisions).CONCLUSION: Use of combined TACE-LITT treatment, compared with the use of TACE or LITT alone, significantly inhibits tumor growth. (c) RSNA, 2005.

9/7/4

DIALOG(R)File 5:Biosis Previews(R)

18480357 BIOSIS NO.: 200510174857

Trimodal cancer treatment: Beneficial effects of combined antianglogenesis, radiation, and chemotherapy

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JOURNAL: Cancer Research 65 (9): p3643-3655,3633 MAY 1 2005 2005

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DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: It has been suggested that chemotherapy and radiotherapy could favorably be combined with antiangiogenesis in dual anticancer strategy combinations. Here we investigate the effects of a trimodal strategy consisting of all three therapy approaches %%%administered%%%

concurrently. We found that in vitro and in vivo, the antiendothelial and antitumor effects of the triple therapy combination consisting of SU11657 (a multitargeted small molecule inhibitor of vascular endothelial growth factor and platelet-derived growth factor receptor tyrosine kinases), Pemetrexed (a multitargeted folate antimetabolite), and ionizing radiation were superior to all single and dual combinations. The superior effects in human umbilical vein endothelial cells and tumor cells (A431) were evident in cell proliferation, migration, tube formation, clonogenic survival, and apoptosis assays (sub-G, and caspase-3 assessment). Exploring potential effects on cell survival signaling, we found that radiation and chemotherapy induced endothelial cell Akt phosphorylation, but SU11657 could attenuate this process in vitro and in vivo in A431 human tumor xenografts growing s.c. on BALB/c nu/nu mice. Triple therapy further decreased tumor cell proliferation (Ki-67 index) and vessel count (CD31 staining), and induced greater tumor growth delay versus all other therapy regimens without increasing apparent toxicity. When testing different treatment schedules for the A431 tumor, we found that the regimen with radiotherapy (7.5 Gy single dose), given after the institution of SU11657 treatment, was more effective than radiotherapy preceding SU11657 treatment. Accordingly, we found that SU11657 markedly reduced intratumoral %%%interstitial%%% fluid pressure from 8.8 2.6 to 4.2 1.5 mm Hg after 1 day. Likewise, quantitative T2-weighed %%%magnetic%%% resonance imaging measurements showed that SU11657-treated mice had reduced intratumoral edema. Our data indicates that inhibition of Akt signaling by antiangiogenic treatment with SU11657 may result in: (a) normalization of tumor blood vessels that cause prerequisite physiologic conditions for subsequent radio/chemotherapy, and (b) direct resensitization of endothelial cells to radio/ chemotherapy. We conclude that trimodal cancer therapy combining antiangiogenesis, chemotherapy, and radiotherapy has beneficial molecular and physiologic effects to emerge as a clinically relevant antitumor strategy.

9/7/5

18368997 BIOSIS NO.: 200510063497

MR imaging-guided %%%interstitial%%% photodynamic laser therapy for advanced head and neck tumors

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JOURNAL: AJNR 26 (5): p1193-1200 MAY 05 2005

ISSN: 0195-6108

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Photodynamic therapy (PDT) is a site-specific tumor treatment involving the %%%administration%%% of a photosensitizer activated by the local application of light. In %%%interstitial%%% PDT (IPDT), multiple laser fibers are inserted into the depth of the tumor. Image guidance is essential for accurate, safe, and uniform light delivery. We report a novel technique of IPDT for advanced head and neck tumors involving an open interventional MR system. Initial results are encouraging, with minimal procedural morbidity, successful palliation of symptoms, and prolongation of expected survival time.

9/7/6

DIALOG(R)File 5:Biosis Previews(R)

17980593 BIOSIS NO.: 200400351382

AEE788: A dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity

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JOURNAL: Cancer Research 64 (14): p4931-4941 July 15, 2004 2004
MEDIUM: print
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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Aberrant epidermal growth factor receptor (EGFR) and ErbB2 expression are associated with advanced disease and poor patient prognosis in many tumor types (breast, lung, ovarian, prostate, glioma, gastric, and squamous carcinoma of head and neck). In addition, a constitutively active EGFR type III deletion mutant has been identified in non-small cell lung cancer, glioblastomas, and breast tumors. Hence, members of the EGFR family are viewed as promising %%%therapeutic%%% targets in the fight against cancer. In a similar vein, vascular endothelial growth factor (VEGF) receptor kinases are also promising targets in terms of an antiangiogenic treatment strategy. AEE788, obtained by optimization of the 7H-pyrrolo(2,3-d)pyrimidine lead scaffold, is a potent combined inhibitor of both epidermal growth factor (EGF) and VEGF receptor tyrosine kinase family members on the isolated enzyme level and in cellular systems. At the enzyme level, AEE788 inhibited EGFR and VEGF receptor tyrosine kinases in the nM range IC50: EGFR 2 nm, ErbB2 6 nm, KDR 77 nm, and Flt-159 nm). In cells, growth factor-induced EGFR and ErbB2 phosphorylation was also efficiently inhibited (IC50s: 11 and 220 nm, respectively). AEE788 demonstrated antiproliferative activity against a range of EGFR and ErbB2-overexpressing cell lines (including EGFRvIII-dependent lines) and inhibited the proliferation of epidermal growth factor- and VEGF-stimulated human umbilical vein endothelial cells. These properties, combined with a favorable pharmacokinetic profile, were associated with a potent antitumor activity in a number of animal models of cancer, including tumors that overexpress EGFR and or ErbB2. Oral %%%administration%%% of AEE788 to tumor-bearing mice resulted in high and persistent compound levels in tumor tissue. Moreover, AEE788 efficiently inhibited growth factor-induced EGFR and ErbB2 phosphorylation in tumors

for >72 h, a phenomenon correlating with the antitumor efficacy of intermittent treatment schedules. Strikingly, AEE788 also inhibited VEGF-induced angiogenesis in a marine implant model. Antiangiogenic activity was also apparent by measurement of tumor vascular permeability and %%%interstitial%%% leakage space using dynamic contrast enhanced %%%magnetic%%% resonance imaging methodology. Taken together, these data indicate that AEE788 has potential as an anticancer agent targeting deregulated tumor cell proliferation as well as angiogenic parameters. Consequently, AEE788 is currently in Phase I clinical trials in oncology.

9/7/7

17970145 BIOSIS NO.: 200400340934

Decrease in tumor apparent permeability-surface area product to a MRI macromolecular contrast medium following angiogenesis inhibition with correlations to cytotoxic drug accumulation

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JOURNAL: Microcirculation (New York) 11 (5): p387-396 July 2004 2004
MEDIUM: print
ISSN: 1073-9688 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: New strategies for cancer therapy include the combination of angiogenesis inhibitors with cytotoxins. However, angiogenesis inhibitors may alter tumor microvessel structure and transendothelial permeability thereby reducing tumoral delivery of cytotoxic agents. The aim of this study was to estimate quantitatively

the apparent permeability-surface area product (KPS) in tumors to a macromolecular contrast medium (MMCM), to follow changes in KPS induced by antibodies to vascular endothelial growth factor (anti-VEGF), and to correlate the findings with tumor accumulation of cisplatin, a highly protein-bound cytotoxin, and 5-fluorouracil (5-FU), a small unbound cytotoxin. Methods: Dynamic MRI enhanced with a MMCM (albumin-(Gd-DTPA)30) was analyzed using a two-compartment tumor tissue model (plasma and %%%interstitial%%% water) to quantitatively estimate KPS. These estimates of KPS were correlated with cytotoxic drug accumulations in the tumors. Results: Anti-VEGF treatment reduced KPS to MMCM in tumor tissue from 0.013 mL h-1 cm-3 (n = 9) at baseline to 0.003 mL h-1 cm-3 (n = 9) 24 h later (p .05). The KPS values correlated significantly (r2 = .78; p .0001) with the tumor cisplatin accumulation. No correlation (r2 = .001; p = .89) was found between KPS and tumor accumulation of the substantially smaller 5-FU molecule. Conclusions: MMCM-enhanced MRI can be used to detect and estimate changes in KPS to this contrast agent following a single dose of anti-VEGF antibody. The decline in KPS induced by this inhibitor of angiogenesis is associated with reduced tumor concentration of a protein-bound cytotoxin, similar in molecular weight to the contrast agent. MRI assays of microvascular status as performed here may be useful to clinically monitor responses to anti-angiogenesis drugs and to optimize the choice and timing of cytotoxic drug %%%administration%%%.

9/7/8

17917713 BIOSIS NO.: 200400288470

Drug delivery systems for brain tumor therapy

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JOURNAL: Current Pharmaceutical Design 10 (12): p1341-1353 2004 2004
MEDIUM: print

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RECORD TYPE: Citation
LANGUAGE: English

9/7/9

17815198 BIOSIS NO.: 200400182884

Radiotherapy and hyperthermia in the treatment of patients with locally advanced prostate cancer: Preliminary results.

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JOURNAL: BJU International 93 (1): p36-41 January 2004 2004
MEDIUM: print
ISSN: 1464-4096 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: OBJECTIVE To report an interim clinical evaluation of combined external beam irradiation (EBRT) and %%%interstitial%%% or regional hyperthermia in the treatment of locally advanced prostate cancer. PATIENTS AND METHODS From 1997 to 2001, 26 patients with T3-4/NX/OMO prostate carcinoma were treated with a combination of conformal EBRT and hyperthermia. Fourteen patients received five weekly regional hyperthermia treatments within an optimization (phase II) study, using the coaxial transverse electrical %%%magnetic%%% system. Twelve patients received one %%%interstitial%%% hyperthermia treatment within a feasibility study (phase I), using the multi-electrode current source system. Irradiation was delivered using a conformal three-field

technique, %%%administering%%% 70 Gy in 2-Gy fractions in 7 weeks. RESULTS The mean initial prostate-specific antigen level was 26 ng/mL. Three patients had a T4 and 23 a T3 tumour; the tumours were classified as well (four), moderately (16) and poorly (six) differentiated. The mean follow-up was 36 months. In the combined treatments there was no toxicity of more than grade 2. In regional hyperthermia the mean index temperature (T90 and T50, i.e. exceeded by 90% and 50% of the measurements) was 40.2degreeC and 40.8degreeC, and for %%%interstitial%%% hyperthermia 39.4degreeC and 41.8degreeC, respectively. All patients survived; seven patients had a biochemical relapse (27%), three in the regional and four in the %%%interstitial%%% group. The actuarial probability of freedom from biochemical relapse was 70% at 36 months for all patients together, 79% for regional and 57% for %%%interstitial%%%. No factors were found that could be used to predict relapse. CONCLUSIONS The clinical outcome in these patients with advanced localized prostate cancer seems to compare favourably with most series using irradiation alone, and the treatment caused no severe complications.

9/7/10

DIALOG(R)File 5:Biosis Previews(R)

16245652 BIOSIS NO.: 200100417491

Acute metabolic alkalosis enhances response of C3H mouse mammary tumors to the weak base mitoxantrone

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JOURNAL: Neoplasia (New York) 3 (3): p227-235 May-June, 2001 2001

MEDIUM: print

ISSN: 1522-8002

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Uptake of weak acid and weak base chemotherapeutic drugs by tumors is greatly influenced by the tumor extracellular/ %%%interstitial%%% pH (pHe), the intracellular pH (pHi) maintained by the tumor cells, and by the ionization properties of the drug itself. The acid-outside plasmalemmal pH gradient in tumors acts to exclude weak base drugs like the anthracyclines, anthraquinones, and vinca alkaloids from the cells, leading to a substantial degree of "physiological drug resistance" in tumors. We have induced acute metabolic alkalosis in C3H . tumor-bearing C3H/hen mice, by gavage and by intraperitoneal (i.p.) %%%administration%%% of NaHCO3. 31P %%%magnetic%%% resonance spectroscopic measurements of 3-aminopropylphosphonate show increases of up to 0.6 pH units in tumor pHe, and 0.2 to 0.3 pH units in hind leg tissue pHe, within 2 hours of i.p. %%%administration%%% of NaHCO3. Theoretical calculations of mitoxantrone uptake into tumor and normal (hind leg) tissue at the measured pHe and pHi values indicate that a gain in %%%therapeutic%%% index of up to 3.3-fold is possible with NaHCO3 pretreatment. Treatment of C3H tumor-bearing mice with 12 mg/kg mitoxantrone resulted in a tumor growth delay of 9 days, whereas combined NaHCO3-mitoxantrone therapy resulted in an enhancement of the TGD to 16 days.

15589856 BIOSIS NO.: 200000308169
Permanent iodine-125 %%%interstitial%%% implants for the treatment of recurrent glioblastoma multiforme
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JOURNAL: Neurosurgery (Baltimore) 46 (5): p1123-1130 May, 2000 2000
MEDIUM: print

ISSN: 0148-396X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: OBJECTIVE: Brachytherapy with temporary implants may prolong survival in patients with recurrent glioblastoma multiforme (GBM), but it is associated with relatively high costs and morbidity. This study reports the time to progression and survival after permanent implantation of iodine-125 seeds for recurrent GBM and examines factors predictive of outcome. METHODS: Forty patients with recurrent GBM were treated with maximal resection plus permanent placement of iodine-125 seeds into the tumor bed. A total dose of 120 to 160 Gy was %%%administered%%%, and patients were followed up with %%%magnetic%%% resonance imaging scans every 2 to 3 months. RESULTS: Actuarial survival from the time of implantation was 47 weeks, with 7 of 40 patients still alive at a median of 59 weeks after implantation. Survival was significantly better for patients younger than 60 years, and a trend for longer survival was demonstrated with gross total resection and tumors with a low MIB-1 (a nuclear antigen present in all cell cycles of proliferating cells) staining index. Median time to progression was 25 weeks and, on multivariate analysis, was favorably influenced by gross total resection and patient age younger than 60 years. After implantation, 27 of 30 patients with failure had a local component to the failure. No patient developed symptoms attributable to radiation necrosis or injury. CONCLUSION: Permanent iodine-125 implants for recurrent GBM result in survival comparable with that described in previous reports on temporary implants, but with less morbidity. Results are most favorable for patients who are younger than 60 years, and who undergo gross total resection. Despite this aggressive treatment, most patients die as a consequence of locally recurrent disease.

15141292 BIOSIS NO.: 199900400952

MRI guidance of infra-red laser liver tumour ablations, utilising an open MRI configuration system: Technique and early progress

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JOURNAL: Journal of Hepatology 31 (2): p347-353 Aug., 1999 1999

MEDIUM: print

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background/Aims: Primary and secondary liver tumours are a common clinical problem, with a poor prognosis in most cases. Surgical resection offers the best outcome, but is only appropriate for the minority. Thermal ablation techniques have been described, but the lack of an optimal means of monitoring has limited their use. We undertook a pilot study to assess the feasibility and safety of an integrated MR-guided laser thermoablation technique under local anaesthesia using a real-time colourisation thermal monitoring technique in a newly developed open MR scanner. Methods: Liver tumours were punctured after the %%%administration%%% of intravenous Mangafodipir trisodium (MnDPDP) using real-time MR image guidance under local or general anaesthesia, and treated using a water-cooled %%%interstitial%%% fibre and a Nd-YAG laser source. Twenty-seven procedures were performed in 12 patients. Therapy was monitored using a real-time MR colourisation sequence. Thermoablation was followed by a colour change in a region of interest. Results: Thermal lesions of mean size 3 cm in diameter were produced with a maximum size of 5 cm. Eight out of 12 patients were discharged the next day with few significant complications. Repeat procedures have been performed in seven of 12 patients. Two patients with lesions of 3 cm diameter have had complete tumour ablation with only one procedure. Conclusion: Percutaneous laser thermoablation for liver tumours performed as an integrated one-step technique in an open configuration MR scanner is described. It can be safely perfomed under local anaesthesia in the

majority of patients, with few side effects. MR control shows the site and size of the evolving thermal lesions, allowing appropriate action to be taken in terms of further burns, time of application and power applied.

9/7/13
DIALOG(R)File 5:Biosis Previews(R)

14261732 BIOSIS NO.: 199800055979
Advanced colloid-based systems for efficient delivery of drugs and diagnostic agents to the lymphatic tissues
AUTHOR: Moghimi S M (Reprint); Rajabi-Siahboomi A R
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JOURNAL: Progress in Biophysics and Molecular Biology 65 (3): p221-249 May, 1996 (1997) 1996
MEDIUM: print
ISSN: 0079-6107
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

9/7/14
DIALOG(R)File 5:Biosis Previews(R)

14100058 BIOSIS NO.: 199799734118
Churg-Strauss syndrome with cerebral seizures and terminal renal failure
AUTHOR: Terjung B (Reprint); Paar W D (Reprint); Schepke M (Reprint); Klehr H U (Reprint); Hufnagel A; Sauerbruch T (Reprint)
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JOURNAL: DMW (Deutsche Medizinische Wochenschrift) 122 (27): p853-858 1997 1997

ISSN: 0012-0472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German

ABSTRACT: History and clinical findings: A 67-year-old man with known bronchial asthma was admitted to hospital because of deteriorating general state of health, fever, progressive renal failure and confusional states. Investigations: Erythrocyte sedimentation rate was 70/95 mm and the concentration of C-reactive protein raised to 30 mg/dl. WBC count was 19,000/mu-l with 39% eosinophilia. Anticytoplasmatic antibodies (cANCA) had a high titre (1:160). On admission the creatinine level was 5.6 mg/dl. Renal biopsy indicated marked glomerular and tubulo-%%%interstitial%%% scarring. Chest radiograms showed transient pulmonary infiltrates. Churg-Strauss syndrome (CSS) was diagnosed on the basis of the clinical and biochemical findings. Treatment and course: Haemodialysis was instituted to counteract the renal failure with water retention. Inflammatory parameters and clinical symptoms rapidly responded to %%%administration%%% of corticosteroids (prednisolone, initially 250 mg/d for 3 days, then 150 mg/d for 5 days followed by slowly decreasing doses). Two weeks after starting prednisolone he had secondary generalised seizures. %%%Magnetic%%% resonance imaging (MRI) of the skull demonstrated marked hyperintense focal changes which in their pattern were characteristic of cerebral vasculitis. As a steroid-refractory condition had to be assumed, cyclophosphamide was also given (100 mg/d). Within 6 weeks the clinical symptoms gradually regressed and the MRI changes became practically normal. Conclusion: Early combined immunotherapy should be given if CSS runs a complicated course, rather than the usually recommended corticosteroid monotherapy.

13311483 BIOSIS NO.: 199698779316
Increasing volume of distribution to the brain with %%%interstitial%%%

infusion: Dose, rather than convection, might be the most important factor

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JOURNAL: Neurosurgery (Baltimore) 38 (4): p746-754 1996 1996

ISSN: 0148-396X

DOCUMENT TYPE: Article

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LANGUAGE: English

ABSTRACT: The volume of distribution in tissue (V-t) that can be achieved by direct %%%interstitial%%% infusion of %%%therapeutic%%% agents into brain is limited. The maintenance of a pressure gradient during %%%interstitial%%% infusion to establish fluid convection has been shown to increase the V-t of small, medium, and large molecules. We have used monocrystalline iron oxide nanocompounds, superparamagnetic particles of sizes the same order of magnitude as virions, to investigate the effect of dose, the volume of infusate, and the time of infusion on the distribution of large molecules in rodent brain. Our initial study in rats (n = 6) replicated the results of a previously described report of convection-enhanced delivery in cats. At a constant rate and concentration, the V-t increased in a linear fashion, proportional to the increases in time, volume, and dose. When using a constant rate and a constant concentration, however, it is unclear which variable or variables (dose, volume, infusion time) have the greatest influence on this effect. Therefore, we assessed each variable independently (n = 12). When the iron dose was increased from 5.3 to 26.5 mu-g, there was a three- to fivefold increase in the V-t, depending on the volume and time of infusion (2 mu-l/20 min, 24 mu-l/20 min, or 24 mu-l/120 min) (P lt 0.001). When the volume of infusate was increased from 2 to 24 mu-l, at an infusion time of 20 minutes and a dose of either 5.3 or 26.5 mu-g, there was a 43 or 52% decline in the V-t, respectively (P = 0.018). When the time for the infusion of 24 mu-l was increased from 20 to 120 minutes, there was a 79% increase in the V-t at a dose of 26.5 mu-g but no change in the V-t at a dose of 5.3 mu-g. The effect associated with

infusion time was not significant (P = 0.113). %%%Magnetic%%% resonance imaging was performed to document the distribution of monocrystalline iron oxide nanocompounds in vivo, and histochemical staining for iron was used to document the distribution of monocrystalline iron oxide nanocompounds in tissue sections. The V-t for both methods was calculated by computer image analysis, and the correlation between %%%magnetic%%% resonance and histological volumes was determined (r-2 = 0.93). On the basis of this model, we suggest that dose, rather than convection, might be the most important variable in maximizing the V-t and improved distribution might be achieved by %%%administering%%% an increased concentration of agent.

9/7/16

11808760 BIOSIS NO.: 199395111026

Intraoperative high-dose rate %%%interstitial%%% irradiation of hepatic metastases from colorectal carcinoma: Results of a phase I-II trial

AUTHOR: Thomas David S (Reprint); Nauta Russell J; Rodgers James E; Popescu George F; Nguyen Huy; Lee Thomas C; Petrucci Peter E; Harter K William; Holt Richard W; Dritschilo Anatoly

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JOURNAL: Cancer (Philadelphia) 71 (6): p1977-1981 1993
ISSN: 0008-543X
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. Resection of liver metastases from colorectal carcinoma can be curative. Unresectable but liver-confined metastases might be ablated by high-dose radiation with a similar curative result. Methods. At Georgetown University Hospital, 22 patients with unresectable hepatic metastases from colorectal carcinoma underwent 24 %%%interstitial%%% irradiation procedures at laparotomy in a Phase I-II

study. A single dose was %%%administered%%% with a high-dose rate iridium-192 afterloader. Dose to the tumor periphery was 20 Gy, 25 Gy, and 30 Gy in 13, 9, and 2 procedures, respectively. Results. No acute or chronic radiation toxicity has occurred at a median follow-up of 11 months. Median actuarial local control at irradiated sites was 8 months, with 26% actuarial local control at 26 months by computed tomography (CT) or %%%magnetic%%% resonance imaging (MRI) scanning. In the two patients undergoing two procedures each, a second biopsy of previously irradiated areas demonstrated tumor eradication. Conclusions. This innovative, radical approach to unresectable colorectal hepatic metastases proved safe. Additional study is needed to determine whether %%%interstitial%%% irradiation is as effective as surgical resection, or whether it alters the natural history of the disease or longevity.

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10/7/1
DIALOG(R)File 5:Biosis Previews(R)

19320991 BIOSIS NO.: 200600666386
Are %%%gadolinium%%%-based contrast media nephrotoxic? A renal biopsy study
AUTHOR: Akgun Hulya; Gonlusen Gulfiliz; Cartwright Joiner; Suki Wadi N; Truong Luan D (Reprint)
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JOURNAL: Archives of Pathology & Laboratory Medicine 130 (9): p1354-1357 SEP 2006 2006
ISSN: 0003-9985
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Gadolinium%%%-based contrast media were originally introduced as alternatives to iodinated media for %%%magnetic%%% resonance imaging.

Although originally thought to be non-nephrotoxic, %%%gadolinium%%%-based contrast media have recently been reported to be associated with acute renal failure; the mechanism and the underlying renal injury are not completely understood. We report what is, to our knowledge, the first renal biopsy in this context. A 56-year-old patient underwent 2 consecutive vascular imaging procedures in conjunction with %%%gadolinium%%%-based contrast medium %%%administration%%%. A few days later, the patient developed acute renal failure. A renal biopsy showed acute tubular cell injury including patchy tubular cell necrosis, tubular cell degeneration, and marked proliferation of tubular cells, together with mild %%%interstitial%%% edema and %%%interstitial%%% inflammation, but without significant glomerular or vascular changes. During supportive therapy, renal function was partially regained. This case emphasizes the potential nephrotoxicity of %%%gadolinium%%%-based contrast media and suggests that the nephrotoxicity is related to potentially reversible acute tubular cell injury.

10/7/2

19103535 BIOSIS NO.: 200600448930

Simultaneous sustained release of fludarabine monophosphate and Gd-DTPA from an %%%interstitial%%% liposome depot in rats: potential for indirect monitoring of %%%drug%%% release by %%%magnetic%%% resonance imaging

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ABSTRACT: Introduction: Cytostatic depot preparations are interstitially %%%administered%%% for local chemotherapy and prevention of tumor recurrence. It would be of interest to monitor in patients as to when, to what extent, and exactly where, the %%%drug%%% is actually released. Liposomes containing a hydrophilic cytostatic and a hydrophilic contrast agent might be expected to release both agents simultaneously. If so, then %%%drug%%% release could be indirectly followed by monitoring contrast enhancement at the injection site. Methods: Multivesicular liposomes containing the antimetabolite fludarabine monophosphate and the %%%magnetic%%% resonance imaging (MRI) contrast agent Gd-DTPA were subcutaneously injected in rats and both agents were monitored at the injection site for 6 weeks by F-19 nuclear %%%magnetic%%% resonance spectroscopy (MRS) in vivo and contrast-enhanced H-1 MRI (T (1w) 3D FLASH), respectively, in a 1.5-T whole-body tomograph. The MRS and MRI data were analyzed simultaneously by pharmacokinetic modeling using NONMEM. Results: During an initial lag time, the amount of %%%drug%%% at the injection site stayed constant while the contrast-enhanced depot volume expanded beyond the volume injected. %%%Drug%%% amount and depot volume then decreased in parallel. Lag time and elimination half-life were 9 and 6 days, respectively, in three animals, and were about 50% shorter in another animal where the depot split into sub-depots. Conclusion: The preliminary data in rats suggest that simultaneous release of a hydrophilic cytostatic and a hydrophilic contrast agent from an %%%interstitial%%% depot can be achieved by encapsulation in liposomes. Thus, there seems to be a potential for indirect %%%drug%%% monitoring through imaging.

10/7/3
DIALOG(R)File 5:Biosis Previews(R)

18343402 BIOSIS NO.: 200510037902
%%%Interstitial%%% %%%magnetic%%% resonance lymphography using %%%gadolinium%%%-ethoxybenzyl-diethylenetriamine pentaacetic acid in rabbits with lymph node metastasis

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JOURNAL: Investigative Radiology 40 (5): p306-312 MAY 05 2005
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LANGUAGE: English

ABSTRACT: Rationale and Objectives: To investigate the dose dependency of %%%gadolinium%%%-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) for %%%interstitial%%% %%%magnetic%%% resonance (MR) lymphography and the detection of lymph node metastasis in rabbits.Methods: Eighteen VX2 tumor-bearing rabbits were subjected to MR lymphography using clinical MRI equipment. The enhancement of popliteal lymph nodes was studied in these rabbits before and at 2.5 to 10 minutes after the subcutaneous %%%administration%%% of 4, 8, or 17 mu mol Gd/kg of Gd-EOB-DTPA in TSE and 3D-FLASH (n = 6). Signal-to-noise ratio and contrast-to-noise ratio were statistically compared between each group by the Tukey test. After MR imaging, the popliteal lymph nodes were removed, and sections were prepared for microscopic examination.Results: In the histologic findings, all metastases (3-12 mm) in the popliteal lymph nodes were detected by 3D-FLASH images. Gd-EOB-DTPA-enhanced T1WI showed a hypointense region for metastasis and a hyperintense region for nontumor regions, although the lymph nodes containing metastasis were detected as a hyperintense region by conventional PDWI and T2WI. Signal enhancement of the nontumor regions and contrast between the nontumor regions and metastasis showed dose dependency and reached a plateau at 8 mu mol Gd/kg on T1WI (signal-to-noise ratio: 13.9 1.6; contrast-to-noise ratio: -12.7 1.7).Conclusions: This study showed that %%%interstitial%%% MR lymphography with Gd-EOB-DTPA can detect metastasis and that the optimal dose in rabbits is 8 mu mol Gd/kg as a subcutaneous application.

DIALOG(R)File 5:Biosis Previews(R)

16826039 BIOSIS NO.: 200200419550
Non-invasive %%%magnetic%%% resonance imaging (MRI) of vascular parameters affected by VEGF-receptor tyrosine kinase inhibition in a human xenograft model
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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p1081-1082 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406
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LANGUAGE: English

10/7/5
DIALOG(R)File 5:Biosis Previews(R)

16708739 BIOSIS NO.: 200200302250
Intrathecal %%%gadolinium%%% (gadopentetate dimeglumine) enhanced %%%magnetic%%% resonance myelography and cisternography: Results of a multicenter study
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JOURNAL: Investigative Radiology 37 (3): p152-159 March, 2002 2002

MEDIUM: print
ISSN: 0020-9996
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: RATIONALE AND OBJECTIVES: This cooperative multicenter human study was designed to evaluate the safety, %%%magnetic%%% resonance (MR) imaging characteristics, and clinical response to a single %%%gadolinium%%% contrast agent: gadopentetate dimeglumine. MATERIAL AND METHODS: Ninety-five patients (age range: 1 month to 78 years; sex: 50 males, 45 females) were included in this prospective study. The patients presented clinically with a variety of cranial or spinal signs and symptoms for which an intrathecal contrast myelogram or cisternogram was requested by clinical staff. Via lumbar puncture (20-25 g needle), 3 to 5 mL/ml of cerebrospinal fluid were withdrawn and mixed with a single volume of 0.5 (n=63), 0.7 (n=13), 0.8 (n=12), or 1.0 (n=7) cc/mL of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany). This was then injected into the subarachnoid space, and the needle was removed. Immediate and delayed (up to 96 hours) T1- and T2-weighted MR imaging was performed on super conductive, high-field (1.0-1.5 tesla) imaging units in two or three planes. All patients were hospitalized for an observation period of 24 hours following the procedure, and follow-up neurologic examinations were performed serially for 6 to 12 months afterward. RESULTS: No patient manifested gross behavioral changes, neurologic alterations, or seizure activity at any time following the procedure. Nineteen patients (20%) experienced postural postlumbar puncture headache, six patients had nausea (6%), and two patients had episodes of vomiting (2%), all which resolved within the first 24 hours of the lumbar puncture with conservative bed rest. CONCLUSION: This cooperative study demonstrates the general safety and feasibility of low dose (0.5-1.0 mL/ml) intrathecal gadopentetate dimeglumine %%%administration%%%. The potential useful clinical applications include the evaluation of obstructions and communications of the various subarachnoid spaces, spontaneous or traumatic/postsurgical craniospinal cerebrospinal fluid leaks, and subarachnoid space CSF flow and parenchymal CNS %%%interstitial%%% diffusion dynamics. This worldwide

cooperative study seeks to progressively perform human studies for further definitive evaluation of the practical clinical applications, of the relationship of this technique to other imaging studies and modalities, and the long-term safety of the procedure in a larger number of subjects.

15996634 BIOSIS NO.: 200100168473
%%%Interstitial%%% MR lymphography with a conventional extracellular %%%gadolinium%%%-based agent: Assessment in rabbits
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JOURNAL: Radiology 218 (3): p664-669 March, 2001 2001
MEDIUM: print
ISSN: 0033-8419
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PURPOSE: To evaluate gadoterate meglumine as a contrast agent for %%%interstitial%%% %%%magnetic%%% resonance (MR) lymphography in combination with an adapted fast three-dimensional (3D) MR sequence. MATERIALS AND METHODS: In 12 New Zealand White rabbits, 0.5 mL of undiluted gadoterate meglumine was injected subcutaneously into the dorsal foot pad (n = 9) or the foreleg (n = 3) bilaterally. Immediately after %%%administration%%%, a slight massage was performed at the injection site. Imaging was performed with a 3D spoiled gradient-recalled echo sequence (6.7/1.6 (repetition time msec/echo time msec); field of view, 28.0 X 19.6; two signals acquired) similar to that used for 3D MR angiography. Thus, 3D maximum intensity projection images could be obtained. Images were obtained before injection and 5, 15, 30, 60, and 120 minutes after injection. RESULTS: In the hind legs, as many as four

successive lymph node groups were depicted with maximum enhancement after 5-15 minutes for the popliteal lymph node group, 15-30 minutes for the inguinal lymph group, and 30-60 minutes for the iliac-paraaortal lymph node group; the iliac-paraaortal lymph node group was not consistently enhanced. In the forelegs, four successive lymph node groups, including axillary and mediastinal lymph node groups, showed marked %%%gadolinium%%% uptake, with maximum enhancement 5-15 minutes after injection. CONCLUSION: As a widely tested positive enhancing T1 contrast agent with favorable safety features, gadoterate meglumine allows the depiction of three to four successive lymph node groups early after subcutaneous injection. With the sequence used, 3D MR lymphangiograms can be obtained.

15142417 BIOSIS NO.: 199900402077
Infarcted myocardium in pigs: MR imaging enhanced with slow-%%%interstitial%%%-diffusion %%%gadolinium%%% compound P760
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JOURNAL: Radiology 212 (2): p467-473 Aug., 1999 1999
MEDIUM: print
ISSN: 0033-8419
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: PURPOSE: To assess the value of P760, a %%%gadolinium%%% chelate with slow %%%interstitial%%% diffusion and high relaxivity, for %%%magnetic%%% resonance (MR) imaging of acute myocardial infarction in pigs. MATERIALS AND METHODS: First-pass gradient-echo MR imaging and spin-echo MR imaging were performed with P760 and then with gadoterate

meglumine in eight pigs with occlusive acute myocardial infarction. P760 signal intensity enhancement and clearance were compared with those of gadoterate meglumine. RESULTS: The first-pass enhancement ratio of P760 in normal myocardium was higher than that in infarcted myocardium (1.37 + 0.06 (SEM) vs 1.05 + 0.03, P = .03). The myocardial first pass showed a blood pool-like curve for P760. The blood pool enhancement ratio 40 seconds after injection was higher for P760 than for gadoterate meglumine (left ventricular cavity, 1.75 + 0.06 vs 1.45 + 0.06, P = .009). Spin-echo MR imaging showed improved contrast between normal and infarcted myocardium after P760 %%%administration%%%: The ratio before contrast material %%%administration%%% was 0.21 + 0.03, that at 15 minutes was 0.48 + 0.05 (P = .002), and that at 25 minutes was 0.47 + 0.07 (P = .003). CONCLUSION: P760 is an MR imaging contrast agent characterized by low diffusion, a blood pool effect soon after low-dose %%%administration%%%, and fast elimination. This agent is useful for improved myocardial perfusion MR imaging of acute myocardial infarction.

10/7/8

14981376 BIOSIS NO.: 199900241036

Differentiation of alveolitis and pulmonary fibrosis in rabbits with %%%magnetic%%% resonance imaging after intrabronchial %%%administration%%% of bleomycin

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JOURNAL: Investigative Radiology 34 (1): p13-21 Jan., 1999 1999
MEDIUM: print
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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: RATIONALE AND OBJECTIVES. The authors investigate the ability of %%%magnetic%%% resonance imaging to differentiate alveolitis and pulmonary fibrosis by correlating %%%magnetic%%% resonance and pathologic findings. METHODS. Lung damage was induced in 52 rabbits by instillation of 5 mL bleomycin sulfate (10 mg/kg) into a lower-lobe bronchus using a balloon catheter. %%%Magnetic%%% resonance examinations were performed in a group of 7 animals 3 hours after the initial damage, and in groups of 8 animals 24 hours and 8, 14, 30, and 80 days after the initial damage. Control animals were examined 3 hours (n = 5), 24 hours, and 8 days (n = 3 for each), respectively, after the instillation of 5 mL 0.9% sodium chloride. %%%Magnetic%%% resonance imaging at 1.5 T included conventional T1-weighted sequences before and after injection of %%%gadolinium%%%-DTPA (0.1 mmol/kg), and T2-weighted fast spin echo sequences. The signal intensity and contrast enhancement of injured lung were evaluated and compared with the contralateral healthy lung and with the lungs of control animals. All animals were killed immediately after the %%%magnetic%%% resonance examination, and the lungs were removed and fixed before sectioning and staining. RESULTS. There was good correlation between signal intensity and contrast enhancement with %%%magnetic%%% resonance imaging and histologic examination. The early phase of acute alveolitis showed lesions with high signal intensity on both T1- and T2-weighted images and marked contrast enhancement after %%%gadolinium%%% -DTPA %%%administration%%%, whereas in the late fibrotic stage the lesions displayed significantly lower signal intensity and contrast enhancement. CONCLUSION. %%%Magnetic%%% resonance imaging can differentiate between alveolitis and fibrosis by means of signal intensity and contrast enhancement after %%%gadolinium%%%-DTPA %%%administration%%%.

10845536 BIOSIS NO.: 199192091307
FACTORS IN MYOCARDIAL PERFUSION IMAGING WITH ULTRAFAST MRI AND %%%GADOLINIUM%%% DTPA %%%ADMINISTRATION%%%

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JOURNAL: Magnetic Resonance in Medicine 20 (2): p299-305 1991
ISSN: 0740-3194
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RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Ultrafast %%%magnetic%%% resonance imaging (MRI) and first pass observation of an %%%interstitial%%% contrast agent are currently being used to study myocardial perfusion. Image intensity, however, is a function of several parameters, including the delivery of the contrast agent to the interstitium (coronary flow rate and diffusion into the interstitium) and the relaxation properties of the tissue (contrast agent concentration, proton exchange rates, and relative intra- and extracellular volume fractions). In this study, image intensity during gadopentatate dimeglumine (Gd-DTPA) %%%administration%%% with T1-weighted ultrafast MR imaging was assessed in an isolated heart preparation. With increasing Gd-DTPA concentration, the steady-state myocardial image intensity increased but the time to reach steady state remained unchanged, resulting in an increased slope of image intensity change. A range of physiologic perfusion pressures (and resulting coronary flow rates) had insignificant effects on kinetics of Gd-DTPA wash-in or steady-state image intensity, suggesting that diffusion of Gd-DTPA into the interstitium is the rate limiting step in image intensity change with this preparation. Following global ischemia and reperfusion, transmural differences in the slope of image intensity change were apparent. However, the altered steady-state image intensity (due to postischemic edema) makes interpretation of this finding difficult. The studied described here demonstrate that although Gd-DTPA %%%administration%%% combined with ultrafast imaging may be a sensitive indicator of perfusion abnormalities, factors other than perfusion will affect image intensity. Extensive studies will be required before image intensity with this protocol is fully understood.

10/7/10

DIALOG(R)File 5:Biosis Previews(R)

08642510 BIOSIS NO.: 198783121401

COMPARISON OF INITIAL BIODISTRIBUTION PATTERNS OF %%%GADOLINIUM%%%-DTPA AND ALBUMIN-%%%GADOLINIUM%%%-DTPA USING RAPID SPIN ECHO MR IMAGING

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JOURNAL: Journal of Computer Assisted Tomography 11 (2): p306-313 1987

ISSN: 0363-8715

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LANGUAGE: ENGLISH

ABSTRACT: The initial biodistribution patterns of %%%gadolinium%%% -diethylenetriaminepentaacetic acid (Gd-DTPA), an extracellular fluid contrast agent, and human serum albumin, paramagnetically labeled with 19 Gd-DTPA groups and used as an intravascular agent, were compared in the brain, heart, liver, and major mediastinal vessels of rats. Repeated 4 s spin echo images acquired after injection of 0.2 mmol/kg Gd-DTPA demonstrated a maximum enhancement between 15 and 25 s of 57% in brain. 307% in heart, 220% in liver, 83% in subcutaneous tissue, and 380% in slowly flowing blood in mediastinal vascular structures. In the following 55 s there was a continuous decrease (average 45%) in signal intensity in each tissue except brain. Albumin-(Gd-DTPA), injected at a four times lower molar dose (0.045 mmol/kg) with respect to Gd-DTPA, demonstrated maximal enhancement of brain by 34%, heart by 237%, liver by 186%, and blood in mediastinal vessels by 325%. %%%Gadolinium%%%-DTPA, which rapidly diffuses from the small vessels into the %%%interstitial%%% space, was noted to accumulate in solid tissues and subsequently to be partially eliminated within 70 s of %%%administration%%%. Signal

enhancement achieved with albumin-(Gd-DTPA) remained at a constant level over the 70 s observation period. These data further support the notion that albumin-(Gd-DTPA), due to its predominantly intravascular distribution, might be applied advantageously for the assessment of perfusion and blood-volume disorders.

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13/7/1
DIALOG(R)File 5:Biosis Previews(R)

17685882 BIOSIS NO.: 200400053412
Modulation of the pharmacokinetics of macromolecular contrast material by avidin chase: MRI, optical, and inductively coupled plasma mass spectrometry tracking of triply labeled %%%albumin%%%.
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JOURNAL: Magnetic Resonance in Medicine 50 (5): p904-914 November 2003 2003
MEDIUM: print
ISSN: 0740-3194 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The goal of this work was to develop an MRI method for mapping the clearance of %%%interstitial%%% macromolecular plasma proteins after their extravasation from permeable blood vessels. To that end, a well-defined window of exposure to elevated blood levels was generated by inducing rapid clearance of macromolecular contrast material from the blood. Experimental removal of the intravascular component allowed subsequent tracking of clearance from the %%%interstitial%%% compartment in the absence of further contrast extravasation. The contrast material

was based on %%%albumin%%% triply labeled with biotin, fluorescent tag, and Gd-DTPA, allowing optical, inductively coupled plasma mass spectrometry (ICP-MS) and MRI detection. The biotin tag was used here for in vivo chasing of the contrast material from the blood by intravenous administration of avidin. Upon administration of avidin the contrast material disappeared from the blood vessels and was cleared by the liver and spleen as detected by MRI, fluorescence of blood samples and histological sections, and by ICP-MS. Nonbiotinylated fluorescent %%%albumin%%% was not affected by administration of avidin. Contrast material that extravasated from leaky blood vessels in a VEGF overexpressing tumor, prior to administration of avidin, was not cleared by the addition of avidin and showed continued %%%interstitial%%% convection. Thus, avidin-chase provides an effective tool for in vivo manipulation of the arterial input function by providing experimental control over the rate of clearance of the contrast material from the circulation.

13/7/2

17214523 BIOSIS NO.: 200300173242

Convective distribution of macromolecules in the primate brain demonstrated using computerized tomography and magnetic resonance imaging.

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JOURNAL: Journal of Neurosurgery 98 (3): p584-590 March 2003 2003

MEDIUM: print

ISSN: 0022-3085

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Applicants

no Lonsea

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Object. Convection-enhanced delivery (CED), the delivery and distribution of drugs by the slow bulk movement of fluid in the extracellular space, allows delivery of therapeutic agents to large volumes of the brain at relatively uniform concentrations. This mode of drug delivery offers great potential for the treatment of many neurological disorders, including brain tumors, neurodegenerative diseases, and seizure disorders. An analysis of the treatment efficacy and toxicity of this approach requires confirmation that the infusion is distributed to the targeted region and that the drug concentrations are in the therapeutic range. Methods. To confirm accurate delivery of therapeutic agents during CED and to monitor the extent of infusion in real time, %%%albumin%%%-linked surrogate tracers that are visible on images obtained using noninvasive techniques (iopanoic acid (IPA) for computerized tomography (CT) and Gd-diethylenetriamine pentaacetic acid for magnetic resonance (MR) imaging) were developed and investigated for their usefulness as surrogate tracers during convective distribution of a macromolecule. The authors infused %%%albumin%%%-linked tracers into the cerebral hemispheres of monkeys and measured the volumes of distribution by using CT and MR imaging. The distribution volumes measured by imaging were compared with tissue volumes measured using quantitative autoradiography with (14C)bovine serum %%%albumin%%% coinfused with the surrogate tracer. For in vivo determination of tracer concentration, the authors examined the correlation between the concentration of the tracer in brain homogenate standards and CT Hounsfield units. They also investigated the long-term effects of the surrogate tracer for CT scanning, IPA-%%%albumin%%%, on animal behavior, the histological characteristics of the tissue, and parenchymal toxicity after cerebral infusion. Conclusions. Distribution of a macromolecule to clinically significant volumes in the brain is possible using convection. The spatial dimensions of the tissue distribution can be accurately defined in vivo during infusion by using surrogate tracers and conventional imaging techniques, and it is expected that it will be possible to determine local concentrations of surrogate tracers in voxels of tissue in vivo by using CT scanning. Use of imaging surrogate tracers is a

practical, safe, and essential tool for establishing treatment volumes during high-flow %%%interstitial%%% microinfusion of the central nervous system.

13/7/3

DIALOG(R)File 5:Biosis Previews(R)

17029605 BIOSIS NO.: 200200623116

Overexpression of vascular endothelial growth factor 165 drives peritumor %%%interstitial%%% convection and induces lymphatic drain: Magnetic Resonance imaging, confocal microscopy, and histological tracking of triple-labeled %%%albumin%%%

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JOURNAL: Cancer Research 62 (22): p6731-6739 November 15, 2002 2002

MEDIUM: print

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Increased expression of vascular endothelial growth factor (VEGF) has been associated with increased lymph node metastases. The aim of this work was to determine whether VEGF-induced hyperpermeability affects peritumor %%%interstitial%%% convection and lymphatic drain, thus linking this growth factor with lymphatic function. Noninvasive imaging of lymphatic function induced by vascular hyperpermeability was achieved by following the distribution of %%%albumin%%% triple-labeled with biotin, fluorescein, and %%%gadolinium%%%-diethylene triamine pentaacetic acid. This contrast material allowed for multimodality imaging using magnetic resonance imaging (MRI), confocal microscopy, and histology. Overexpression of VEGF in C6-pTET-VEGF165 tumors, inoculated in hind limbs of nude mice, elevated vascular permeability, %%%interstitial%%%

convection, and lymphatic drain. These were manifested in dynamic MRI measurements by outward flux of the contrast material, the rate of which correlated with tumor volume followed by directional flow toward the popliteal lymph node. Avidin-chase, namely i.v. administration of avidin, was applied for inducing rapid clearance of the intravascular biotinylated contrast material, thus allowing early experimental separation between vascular leak and lymphatic drain. Repeated MRI measurements of the same mice were conducted 48 h after withdrawal of VEGF by addition of tetracycline to the drinking water. VEGF withdrawal decreased tumor blood-plasma volume fraction by 43%, reduced tumor permeability by 75%, and abolished %%%interstitial%%% convection of the contrast material. Histological sections and whole-mount confocal microscopy confirmed VEGF-induced changes in permeability and %%%interstitial%%% accumulation of the contrast material, as well as uptake of the contrast material into peritumor lymphatic vessels. These results revealed a direct link between expression of VEGF165 and peritumor lymphatic drain, thus suggesting a possible role for tumor-derived VEGF in metastatic spread to sentinel lymph nodes.

13/7/4

16266118 BIOSIS NO.: 200100437957

Early changes in vascular physiology of tumors during continuous anti-angiogenic therapy

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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p388 March, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324
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DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

13/7/5
DIALOG(R)File 5:Biosis Previews(R)

14691250 BIOSIS NO.: 199800485497
Direct convective delivery of macromolecules to the spinal cord
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JOURNAL: Journal of Neurosurgery 89 (4): p616-622 Oct., 1998 1998
MEDIUM: print
ISSN: 0022-3085
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Object. Because of the limited penetration of macromolecules across the blood-spinal cord barrier, numerous therapeutic compounds with potential for treating spinal cord disorders cannot be used effectively. The authors have developed a technique to deliver and distribute macromolecules regionally in the spinal cord by using convection in the %%%interstitial%%% space. Methods. The authors designed a delivery system connected to a "floating" silica cannula (inner diameter 100 mum, outer diameter 170 mum) that provides for constant volumetric inflow to the spinal cord. A solution containing %%%albumin%%% that was either unlabeled or labeled with carbon-14 or %%%gadolinium%%% was infused at various volumes (3, 6, 10, 20, 40, or 50 mul) at a rate of 0.1 mul/minute into the spinal cord dorsal columns of nine swine and into the lateral columns of three primates (Macaca mulatta). Volume of distribution (Vd), concentration homogeneity, and percentage of recovery were determined

using scintillation analysis, kurtosis calculation (K), and quantitative autoradiography (six swine), magnetic resonance imaging (one swine and three primates), and histological analysis (all animals). Neurological function was observed for up to 3 days in four of the swine and up to 16 weeks in the three primates. The Vd of 14C-%%%albumin%%% was linearly proportional (R2 = 0.97) to the volume of infusion (Vi) (Vd/Vi = 4.4 + 0.5; (mean standard deviation)). The increases in Vd resulting from increases in Vi were primarily in the longitudinal dimension (R2 = 0.83 in swine; R2 = 0.98 in primates), allowing large segments of spinal cord (up to 4.3 cm; Vi 50 mul) to be perfused with the macromolecule. The concentration across the area of distribution was homogeneous (K = -1.1). The mean recovery of infused %%%albumin%%% from the spinal cord was 85.5 + 5.6%. Magnetic resonance imaging and histological analysis combined with quantitative autoradiography revealed the %%%albumin%%% infusate to be preferentially distributed along the white matter tracts. No animal exhibited a neurological deficit as a result of the infusion.
Conclusions. Regional convective delivery provides reproducible, safe, region-specific, and homogeneous distribution of macromolecules over large longitudinal segments of the spinal cord. This delivery method overcomes many of the obstacles associated with current delivery techniques and provides for research into new treatments of various conditions of the spinal cord.

13/7/6

12700201 BIOSIS NO.: 199598168034

Effects of myocardial water exchange on T-1 enhancement during bolus administration of MR contrast agents

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DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interpretation of first-pass myocardial perfusion studies employing bolus administration of T-1 magnetic resonance (MR) contrast agents requires an understanding of the relationship between contrast concentration and image pixel intensity. The potential effects of myocardial water exchange rates among the intravascular, %%%interstitial%%%, and cellular compartments on this relationship are controversial. We directly studied these issues in isolated, nonbeating canine interventricular septa. Myocardial T-1 was measured three times/s during bolus transit of intravascular (%%%albumin%%%-Gd-DTPA and polylysine-Gd-DTPA) and extracellular (gadoteridol) contrast agents. For polylysine-Gd-DTPA, the peak changes in myocardial 1/T-1 (DELTA-R1) scaled nonlinearly with perfusate contrast concentration whereas a linear relationship would be expected for fast water exchange among the vascular, %%%interstitial%%%, and cellular compartments. For all agents, the peak DELTA-R1 were much smaller than the values expected on the basis of fast myocardial water exchange. The data demonstrate that in isolated myocardial tissue, myocardial T-1 enhancement during bolus administration of contrast can be strongly affected by myocardial water exchange for both intravascular and extracellular MR contrast agents.

13/7/7
DIALOG(R)File 5:Biosis Previews(R)

11849250 BIOSIS NO.: 199396013666
Measurement of capillary permeability to macromolecules by dynamic magnetic resonance imaging: A quantitative noninvasive technique
AUTHOR: Shames David M; Kuwatsuru Ryohei; Vexler Vladimur; Muhler Andreas; Brasch Robert C (Reprint)
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JOURNAL: Magnetic Resonance in Medicine 29 (5): p616-622 1993

ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A simple, linear kinetic model has been developed for the noninvasive assessment of capillary permeability to macromolecules in the rat by dynamic magnetic resonance imaging using %%%albumin%%%-Gd-DTPA. Data required by the model are signal intensity responses from a target tissue and a venous structure such as inferior vena cava before and after bolus intravenous injection of %%%albumin%%%-Gd-DTPA. Additional requirements include an early temporal resolution of approximately one image/min and a blood sample for hematocrit. The model does not require measurement of %%%albumin%%%-Gd-DTPA concentration in either arterial or venous blood. Pilot experiments suggest that this technique is adequate for estimation of the fractional leak rate of macromolecules from plasma to %%%interstitial%%% water as well as tissue plasma volume, the product of which yields a measure of the permeability surface area product of the tissue if the extraction fraction is modest (It 0.2). The technique may be generally applicable to the study of abnormal capillary permeability in humans as well as animals.

13/7/8
DIALOG(R)File 5:Biosis Previews(R)

10696083 BIOSIS NO.: 199191078974
MR IMAGE TIME-INTENSITY RELATIONS IN SPLEEN AND KIDNEY A COMPARATIVE STUDY
OF %%%GADOLINIUM%%% DTPA %%%ALBUMIN%%% %%%GADOLINIUM%%% DTPA AND
%%%GADOLINIUM%%% OXIDE COLLOID
AUTHOR: DALY P F (Reprint); ZIMMERMAN J B; CANNILLO J A; WOLF G L
AUTHOR ADDRESS: MASS GEN HOSP, NMR CENT, BUILD 149, 13TH ST, CHARLESTON,
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JOURNAL: American Journal of Physiologic Imaging 5 (3): p119-124 1990
ISSN: 0885-8276
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Magnetic resonance images were performed using a gradient recalled echo sequence with acquisition of images every 30 s in anesthetized rats before and after intravenous bolus injections of 100 .mu.m/kg GdDTPA, 60 .mu.m/kg %%%albumin%%%-(GdDTPA), and 60 .mu.m/kg Gd2O3 colloid. All three agents caused significant enhancement of the renal cortex, and even greater enhancement of the spleen. GdDTPA showed an early peak at 11 s followed by a wash-out as blood concentrations fell, whereas %%%albumin%%%-(GdDTPA) and Gd2O3 showed sustained tissue enhancement. The enhancement in each organ was equivalent for %%%albumin%%%-(GdDTPA) and Gd2O3 which stay intravascular; but 30% less for GdDTPA which enters the %%%interstitial%%% space. In addition GdDTPA showed an initial enhancement of the renal medulla but then a subsequent loss of signal, whereas %%%albumin%%%-(GdDTPA) resulted in a greater enhancement of the medulla as compared to the cortex. We conclude that time-intensity studies of local tissue response to MR indicators reflect tissue physiological parameters such as perfusion, blood volume, and concentrating ability in a semiquantitative manner.

08642510 BIOSIS NO.: 198783121401
COMPARISON OF INITIAL BIODISTRIBUTION PATTERNS OF %%%GADOLINIUM%%%-DTPA AND %%%ALBUMIN%%%-%%%GADOLINIUM%%%-DTPA USING RAPID SPIN ECHO MR IMAGING
AUTHOR: SCHMIEDL U (Reprint); MOSELEY M E; OGAN M D; CHEW W M; BRASCH R C

AUTHOR ADDRESS: CONTRAST MEDIA LAB, DEP RADIOLOGY, C-309, UNIV CALIFORNIA
AT SAN FRANCISCO, SAN FRANCISCO, CALIFORNIA 94143-0628, USA**USA
JOURNAL: Journal of Computer Assisted Tomography 11 (2): p306-313 1987
ISSN: 0363-8715
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The initial biodistribution patterns of %%%gadolinium%%% -diethylenetriaminepentaacetic acid (Gd-DTPA), an extracellular fluid contrast agent, and human serum %%%albumin%%%, paramagnetically labeled with 19 Gd-DTPA groups and used as an intravascular agent, were compared in the brain, heart, liver, and major mediastinal vessels of rats. Repeated 4 s spin echo images acquired after injection of 0.2 mmol/kg Gd-DTPA demonstrated a maximum enhancement between 15 and 25 s of 57% in brain. 307% in heart, 220% in liver, 83% in subcutaneous tissue, and 380% in slowly flowing blood in mediastinal vascular structures. In the following 55 s there was a continuous decrease (average 45%) in signal intensity in each tissue except brain. %%%Albumin%%%-(Gd-DTPA), injected at a four times lower molar dose (0.045 mmol/kg) with respect to Gd-DTPA, demonstrated maximal enhancement of brain by 34%, heart by 237%, liver by 186%, and blood in mediastinal vessels by 325%. %%%Gadolinium%%%-DTPA, which rapidly diffuses from the small vessels into the %%%interstitial%%% space, was noted to accumulate in solid tissues and subsequently to be partially eliminated within 70 s of administration. Signal enhancement achieved with %%%albumin%%%-(Gd-DTPA) remained at a constant level over the 70 s observation period. These data further support the notion that %%%albumin%%%-(Gd-DTPA), due to its predominantly intravascular distribution, might be applied advantageously for the assessment of perfusion and blood-volume disorders.

? t s16/7/1-16

16/7/1
DIALOG(R)File 5:Biosis Previews(R)

18568468 BIOSIS NO.: 200510262968

Development of nano-sized dendrimer based MR contrast agents for imaging of breast cancer sentinel nodes.

AUTHOR: Brechbiel Martin W (Reprint); Kobayashi Hisataka; Kawamoto Satomi; Sakai Yoshio; Choyke Peter; Morris John; Waldmann Thomas A

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JOURNAL: Abstracts of Papers American Chemical Society 228 (Part 1): pU831 AUG 22 2004 2004

CONFERENCE/MEETING: Meeting of the Division of Chemical Toxicology of the American-Chemical-Society held at the 228th National Meeting of the American-Chemical-Society Philadelphia, PA, USA August 22-26, 2004; 20040822

SPONSOR: Amer Chem Soc, Div Chem Toxicol

ISSN: 0065-7727

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

16/7/2

DIALOG(R)File 5:Biosis Previews(R)

18244097 BIOSIS NO.: 200500151162

Ventilation-synchronous %%%magnetic%%% resonance microscopy of pulmonary structure and ventilation in mice

AUTHOR: Chen Ben T; Yordanov Alexander T; Johnson G Allan (Reprint)

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JOURNAL: Magnetic Resonance in Medicine 53 (1): p69-75 January 2005 2005

MEDIUM: print

ISSN: 0740-3194 _(ISSN print)

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Increasing use of transgenic animal models for pulmonary disease has raised the need for methods to assess pulmonary structure and function in a physiologically stable mouse. We report here an integrated protocol using %%%magnetic%%% resonance microscopy with gadolinium (Gd)-labeled starburst dendrimer (G6-%%%1B4M%%%-Gd, MW = 192 1 kDa, Rh = 5.50 0.04 nm) and hyperpolarized 3 helium (3He) gas to acquire images that demonstrate pulmonary vasculature and ventilated airways in live mice (n = 9). Registered three-dimensional images of1 H and3 He were acquired during breath-hold at 2.0 T using radial acquisition (total acquisition time of 38 and 25 min, respectively). The macromolecular Gd-labeled dendrimer (a half-life of apprx80 min) increased the signal-to-noise by 81 30% in the left ventricle, 43 22% in the lung periphery, and -4 5% in the chest wall, thus increasing the contrast of these structures relative to the less vascular surrounding tissues. A constant-flow ventilator was developed for the mouse to deliver varied gas mixtures of O2 and N2 (or3 He) during imaging. To avoid hypoxemia, instrumental dead space was minimized and corrections were made to tidal volume lost due to gas compression. The stability of the physiologic support was assessed by the lack of spontaneous breathing and maintenance of a constant heart rate. We were able to stabilize the mouse for >8 hr using ventilation of 105 breath/min and apprx0.2 mL/breath. The feasibility of acquiring both pulmonary vasculature and ventilated airways was demonstrated in the mouse lung with inplane spatial resolution of 70 x 70 mum2 and slice thickness of 800 mum.

16/7/3

17916238 BIOSIS NO.: 200400286995

Functional Pulmonary MR Microscopy in Mice

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JOURNAL: FASEB Journal 18 (4-5): pAbst. 638.8 2004 2004
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome Washington, District of Columbia, USA April 17-21, 2004; 20040417
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mouse has become a key animal model to connect genotype to both structural and functional phenotype. As research in functional genomics progresses, the interest in non-invasive assessment of changes in pulmonary structure and function in a physiological stable mouse has increased. We report here the use of %%%magnetic%%% resonance microscopy with gadolinium (Gd) labeled PAMAM starburst dendrimer and hyperpolarized 3Helium (He) gas to acquire pulmonary images in vivo, indicating perfusion and ventilation distribution in the lung. The images (256x256 with 18 mm field of view) were acquired during breath-hold at 2.0 T using a ventilator-gated 3-dimensional radial encoding technique for thin slices (800 (m). A custom-made constant flow ventilator was used to deliver gas mixtures of 23% O2 and 77% N2 during 1H imaging, and 23% O2 and 77% HP 3He during 3He imaging. To avoid hypoxemia, instrumental dead space was minimized and air compression was corrected for tidal volume. Prior to imaging, the Gd-labeled generation-6 dendrimer (G6-%%%1B4M%%% -Gd, MW = 192(1 kDa, Rh = 5.50(0.04 nm) was administered (160 (g in 0.1 ml) via a tail vein as an intravascular contrast agent (half-life of 80 min). We successfully maintained the mouse at a stable condition throughout the study (>6 hours) using ventilation rate of 105 breaths/min and tidal volume of 0.2 ml. The perfusion and ventilation distributions were demonstrated in the 1H (A) and 3He (B) images with in-plane spatial resolution of 70x70 (m 2. Our results demonstrate the feasibility of perfusion and ventilation distribution in the lung using these techniques. The regional distribution can be assessed, which can provide quantitative comparison of pulmonary disease models. This project is

supported by NHLBI R01 HL 055348, NCI R24 CA92656, and NCRR P41 RR05959.

16/7/4

DIALOG(R)File 5:Biosis Previews(R)

16816283 BIOSIS NO.: 200200409794

Dynamic micro-MRI of the micro-circulation in the tumor xenografts using the various sizes of dendrimer-based macromolecular MR contrast agents to evaluate the vascular anatomy and physiology

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p896 March, 2002 2002

MEDIUM: print

CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406

ISSN: 0197-016X

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

16/7/5

DIALOG(R)File 5:Biosis Previews(R)

16756441 BIOSIS NO.: 200200349952

Renal tubular damage detected by dynamic micro-MRI with a dendrimer-based %%%magnetic%%% resonance contrast agent

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Jo Sang-Kyung; Sato Noriko; Saga Tsuneo; Hiraga Akira; Konishi Junji; Hu Susan; Togashi Kaori ; Brechbiel Martin W; Star Robert A

AUTHOR ADDRESS: Metabolism Branch, National Cancer Institute, National

Institutes of Health, 10 Center Drive, Building 10, Room 4N109, MSC 1374, Bethesda, MD, 20892, USA**USA
JOURNAL: Kidney International 61 (6): p1980-1985 June, 2002 2002
MEDIUM: print
ISSN: 0085-2538
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background. A noninvasive technique to evaluate the structure and function of the kidney would be useful to investigate renal diseases, especially acute renal failure. We have developed a novel technique to visualize functional micro-%%%magnetic%%% resonance (MR) images of the mouse kidney with a dendrimer-based macromolecular renal MR contrast agent. Method. Mice were injected with cisplatin or vehicle, then examined three days later by contrast-enhanced, dynamic high-resolution micro-MRI with 160 mum spatial resolution using a 1.5 T clinical MRI unit, a surface coil, and the renal contrast agent G4D-(%%%1B4M%%%-Gd)64. Results. The cortex and outer stripe of the outer medulla of the mouse kidney were clearly visualized in the normal mice. In animals treated with cisplatin, the gradation of tubular damage as assessed by contrast enhanced dynamic MRI correlated with renal function. Conclusion. Contrast-enhanced, dynamic high-resolution micro-MRI with a novel dendrimer-based macromolecular renal MR contrast agent can be a powerful tool for in vivo observation of renal structural and functional damage.

16/7/6
DIALOG(R)File 5:Biosis Previews(R)

16581231 BIOSIS NO.: 200200174742
Rapid accumulation and internalization of radiolabeled herceptin in an inflammatory breast cancer xenograft with vasculogenic mimicry predicted by the contrast-enhanced dynamic MRI with the macromolecular contrast agent G6-(%%%1B4M%%%-Gd)256
AUTHOR: Kobayashi Hisataka (Reprint); Shirakawa Kazuo; Kawamoto Satomi;

Saga Tsuneo; Sato Noriko; Hiraga Akira; Watanabe Ichiro; Heike Yuji; Togashi Kaori; Konishi Junji; Brechbiel Martin W; Wakasugi Hiro

AUTHOR ADDRESS: Metabolism Branch, National Cancer Institute, NIH, 10 Center Drive, Building 10, Room 4N109, Bethesda, MD, 20892, USA**USA

JOURNAL: Cancer Research 62 (3): p860-866 February 1, 2002 2002

MEDIUM: print

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: The rapid blood flow and perfusion of macromolecules in the inflammatory breast cancer xenograft (WIBC-9), which exhibits a "vasculogenic mimicry" type of angiogenesis without the participation of endothelial cells and expresses high levels of the HER-2/neu antigen, was evaluated in mice using 3D-micro-MR angiography using a novel macromolecular MR contrast agent (G6-(%%%1B4M%%%-Gd)256). Herceptin, which recognizes the HER-2/neu antigen and has similar size (10 nm) to G6-(%%%1B4M%%%-Gd)256, accumulated and internalized in the WIBC-9 tumors more quickly than in the control MC-5 tumors that progress with normal angiogenesis. Three dimensional micro-MRI with the G6-(%%%1B4M%%%-Gd)256 macromolecular MRI contrast agent distinguishes between the different types of angiogenesis and is predictive of the rapid accumulation and internalization of Herceptin in the WIBC-9 inflammatory breast cancer xenograft.

16/7/7

16339448 BIOSIS NO.: 200100511287

Novel liver macromolecular MR contrast agent with a polypropylenimine diaminobutyl dendrimer core: Comparison to the vascular MR contrast agent with the polyamidoamine dendrimer core

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Akita Yukio; Mamede Marcelo H;

Konishi Junji; Togashi Kaori; Brechbiel Martin W
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JOURNAL: Magnetic Resonance in Medicine 46 (4): p795-802 October, 2001
2001
MEDIUM: print
ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: As MRI contrast agents, more hydrophobic molecules reportedly accumulate in the liver and thus are potentially useful as liver MRI contrast agents. In this study, a generation-4 polypropylenimine diaminobutane dendrimer (DAB-Am64), which is expected to be more hydrophobic than the generation-4 polyamidoamine dendrimer (PAMAM-G4D), was used to synthesize a conjugate with 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%) (DAB-Am64-(%%%1B4M%%%-Gd)64) for complexing Gd(III) ions. This DAB conjugate quickly accumulated in the liver and its characteristics were studied and compared with those of a PAMAM conjugate (PAMAM-G4D-(%%%1B4M%%%-Gd)64), which is known to be a useful vascular MRI contrast agent, in regard to its availability as a liver MRI contrast agent. DAB-Am64-(%%%1B4M%%%-Gd)64 accumulated significantly more in the liver and less in blood than PAMAM-G4D-(%%%1B4M%%%-Gd)64 ($P<0.001$). Contrast-enhanced MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance liver parenchyma and visualize both portal and hepatic veins of 0.5 mm diameter in mice. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a good candidate for a liver MRI contrast agent.

16294832 BIOSIS NO.: 200100466671

3D MR angiography of intratumoral vasculature using a novel macromolecular MR contrast agent

AUTHOR: Kobayashi Hisataka (Reprint); Sato Noriko; Kawamoto Satomi; Saga Tsuneo; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Magnetic Resonance in Medicine 46 (3): p579-585 September, 2001 2001

MEDIUM: print

ISSN: 0740-3194

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Noninvasive methods to visualize blood flow in the intratumoral vasculature have not previously been studied. In the present study, the use of a novel intravascular MR contrast agent with a generation-6 polyamidoamine dendrimer core (G6-(%%%1B4M%%%-Gd)192; MW: 175kD) was investigated, and the vasculature in experimental tumors was visualized using 3D MR angiography (MRA). Xenografted tumors in nude mice of two different histologies-KT005 (human osteogenic sarcoma) and LS180 (human colon carcinoma)-were used to obtain 3D MRA using G6-(%%%1B4M%%%-Gd)192 and Gd-DTPA. The contrast MR sectional images were correlated with the corresponding histological sections. The intratumoral vasculature in the KT005 tumor was clearly visualized by 3D MRA, which became more evident with the growth of the tumor xenograft. In contrast, the intratumoral vasculature in the LS180 tumor was sparser and much less developed than that in KT005 tumors. Blood vessels with a diameter as small as 100 mum based on histology were visualized using 0.033 mmol Gd/kg of G6-(%%%1B4M%%%-Gd)192. In conclusion, intratumoral vasculature with a 100-mum diameter was visualized better using 3D MRA with G6-(%%%1B4M%%%-Gd)192 than with Gd-DTPA.

16294816 BIOSIS NO.: 200100466655

Novel intravascular macromolecular MRI contrast agent with generation-4 polyamidoamine dendrimer core: Accelerated renal excretion with coinjection of lysine

AUTHOR: Kobayashi Hisataka (Reprint); Sato Noriko; Kawamoto Satomi; Saga Tsuneo; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Magnetic Resonance in Medicine 46 (3): p457-464 September, 2001 2001

MEDIUM: print

ISSN: 0740-3194

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RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: One of the major limitations to macromolecular MRI contrast agents (MRI-CAs) is their slow clearance and associated decreased excretion of gadolinium (Gd(III)). The effect of coinjecting lysine to accelerate renal excretion of a macromolecular MRI-CA (generation-4 PAMAMTM dendrimer (G4D-(%%%1B4M%%%-Gd)64)) was investigated. The biodistribution and urine and fecal excretion in athymic mice was evaluated with and without lysine coinjection. 3D-dynamic-micro-MRI with G4D-(%%%1B4M%%%-Gd)64 was obtained with and without lysine coinjection, and the serial signal intensity (SI) change in the blood and organs was evaluated. When lysine was coinjected, urinary excretion of G4D-(%%%1B4M%%%-Gd)64 increased 5.4-fold compared to that without lysine, resulting in decreased renal accumulation of G4D-(%%%1B4M%%%-Gd)64 from 150% to 40% injected dose per gram ($P < 0.001$). On dynamic MRI with G4D-(%%%1B4M%%%-Gd)64, when lysine was coinjected, the kidney-to-blood SI ratio was significantly lower than that obtained without lysine ($P < 0.001$). When lysine was coinjected, the G4D-(%%%1B4M%%%-Gd)64 was

excreted from the kidney intact.

16/7/10

DIALOG(R)File 5:Biosis Previews(R)

16263615 BIOSIS NO.: 200100435454

Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent of gadolinium neutron capture therapy for intraperitoneal disseminated tumor, which can be monitored by MRI

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Ishimori Takayoshi; Tabassum Haque L; Ono Koji; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Graduate School of Medicine, Kyoto University, Kyoto, Japan **Japan

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p382 March, 2001 2001

MEDIUM: print

CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324

SPONSOR: American Association for Cancer Research

ISSN: 0197-016X

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

16/7/11

DIALOG(R)File 5:Biosis Previews(R)

16230692 BIOSIS NO.: 200100402531

Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent for gadolinium neutron capture therapy of intraperitoneal disseminated tumor which can be monitored by MRI

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato

Noriko; Ishimori Takayoshi; Konishi Junji; Ono Koji; Togashi Kaori;
Brechbiel Martin W
AUTHOR ADDRESS: Department of Diagnostic and Interventional Imagiology, Graduate School of Medicine, Hitachi Medial Co., Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan
JOURNAL: Bioconjugate Chemistry 12 (4): p587-593 July-August, 2001 2001
MEDIUM: print
ISSN: 1043-1802
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Peritoneal carcinomatosis is a late stage in cancer progress, for which no effective therapeutic modality exists. Targeting therapeutic agents to disseminated lesions may be a promising modality for treating peritoneal carcinomatosis. Gadolinium (157,155Gd) is known to generate Auger and internal conversion electrons efficiently by irradiation with a neutron beam. Auger electrons from neutron-activated Gd(III) are strongly cytotoxic, but only when Gd(III) atoms have been internalized into the cells. In the present investigation, we have developed a quickly internalizing tumor-targeting system to deliver large quantities of Gd(III) atoms into tumor cells to generate the Auger emission with an external neutron beam. Simultaneously, one would be able to image its biodistribution by MRI with a shortened T1 relaxation time. Avidin-G6-(%%%1B4M%%%-Gd)254 (Av-G6Gd) was synthesized from generation-6 polyamidoamine dendrimer, biotin, avidin, and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%). The Av-G6Gd was radiolabeled with Gd(III) doped with 153Gd. All of the %%%1B4M%%%'s on the conjugate were fully saturated with Gd(III) atoms. An in vitro internalization study showed that Av-G6Gd accumulated and was internalized into SHIN3 cells (a human ovarian cancer) 50- and 3.5-fold greater than Gd-DTPA (Magnevist) and G6-(%%%1B4M%%%-Gd)256 (G6Gd). In addition, accumulation of Gd(III) in the cells was detected by the increased signal on T1-weighted MRI. A biodistribution study was performed in nude mice bearing intraperitoneally disseminated SHIN3 tumors. Av-G6Gd showed specific accumulation in the SHIN3 tumor (103% ID/g) 366- and 3.4-fold greater

than Gd-DTPA (0.28% ID/g, p<0.001) and G6Gd (30% ID/g, p<0.001) 1 day after i.p. injection. Seventy-eight percent of the tumor-related radioactivity of Av-G6Gd in the SHIN3 tumor was located inside the cells. The SHIN3 tumor-to-normal tissue ratio was greater than 17:1 in all organs and increased up to 638:1 at 1 day after i.p. injection. In conclusion, a sufficient amount (162 ppm) of Av-G6Gd was accumulated and internalized into the SHIN3 cells both in vitro and in vivo to kill the cell using 157/155Gd with external irradiation with an appropriate neutron beam while monitoring with MRI. Thus, Av-G6Gd may be a promising agent for Gd neutron capture therapy of peritoneal carcinomatosis. This reagent also has the potential to permit monitoring of its pharmacokinetic progress with MRI.

16/7/12

16180642 BIOSIS NO.: 200100352481

Dynamic micro-%%%magnetic%%% resonance imaging of liver micrometastasis in mice with a novel liver macromolecular %%%magnetic%%% resonance contrast agent DAB-Am64-(%%%1B4M%%%-Gd)64

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Department of Diagnostic and Interventional Radiology, Graduate School of Medicine, Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan

JOURNAL: Cancer Research 61 (13): p4966-4970 July 1, 2001 2001
MEDIUM: print
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: DAB-Am64-(%%%1B4M%%%-Gd)64 is a newly synthesized macromolecular

liver %%%magnetic%%% resonance imaging (MRI) contrast agent with a polypropylenimine diaminobutane (DAB) dendrimer conjugated with a bifunctional diethylenetriaminepentaacetic acid (DTPA) derivative for complexing Gd(III) atoms. The characteristics of DAB-Am64-(%%%1B4M%%% -Gd)64, which quickly accumulated in the liver, have been reported recently. In the present study, the dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was obtained in the mouse liver metastasis model using colon carcinoma cells to evaluate the ability to visualize the micrometastatic tumors compared with that using Gd-DTPA. The dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance the normal liver parenchyma and visualize micrometastatic tumors of 0.3-mm diameter in the liver of the mice with better contrast than that with Gd-DTPA. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a new liver MRI contrast agent potentially useful for diagnosis of micrometastasis in the liver.

16/7/13

15997101 BIOSIS NO.: 200100168940

3D-micro-MR angiography of mice using macromolecular MR contrast agents with polyamidoamine dendrimer core with reference to their pharmacokinetic properties

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JOURNAL: Magnetic Resonance in Medicine 45 (3): p454-460 March, 2001 2001
MEDIUM: print
ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Four novel macromolecular MRI contrast agents, all of which had the same chemical composition but different molecular weights, were prepared using generation-3, -4, -5, and -6 polyamidoamine (PAMAMTM) dendrimers conjugated with a bifunctional diethylenetriaminepentaacetic acid derivative to change the blood retention, tissue perfusion, and excretion. Size-dependent changes in the pharmacokinetics were observed in the biodistribution study. 153Gd-labeled generation-6 PAMAMTM-conjugates remained in the blood significantly longer than all of the other preparations ($P < 0.001$). The increase in blood-to-organ ratio of the preparations was found to correlate with increasing molecular size ($P < 0.001$). Additionally, 3D-micro MR images and angiography of mice of high quality and detail were obtained using PAMAMTM-(%%%1B4M%%%-Gd)x as a macro-molecular MRI contrast agent with a 1.5-T clinical MRI instrument. Numerous fine vessels of apprx200 mum diameter were visualized on subtracted 3D-MR angiographms with G6D-(%%%1B4M%%%-Gd)192. The quality of the images was sufficient to estimate the microvasculature of cancerous tissue for anti-angiogenesis therapy and to investigate knockout mice.

15970175 BIOSIS NO.: 200100142014

Comparison of the macromolecular MR contrast agents with ethylenediamine-core versus ammonia-core generation-6 polyamidoamine dendrimer

AUTHOR: Kobayashi Hisataka (Reprint); Sato Noriko; Kawamoto Satomi; Saga Tsuneo; Hiraga Akira; Laz Haque Tabassum; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Bioconjugate Chemistry 12 (1): p100-107 January-February, 2001
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DOCUMENT TYPE: Article
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LANGUAGE: English

ABSTRACT: Two novel macromolecular MRI contrast agents based upon generation-6 polyamidoamine dendrimers (G6) of presumed similar molecular size, but of different molecular weight, were compared in terms of their blood retention, tissue distribution, and renal excretion. Two G6s with either ammonia core (G6A) or with ethylenediamine core (G6E), which possessed 192 and 256 exterior primary amino groups, respectively, were used. These dendrimers were reacted with 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%). The G6-%%%1B4M%%% conjugates were reacted with 153Gd for studying biodistribution and blood clearance or Gd(III) for the MRI study. 3D-micro-MR angiography of the mice were taken with injection of 0.033 mmol of Gd/kg of G6A-(%%%1B4M%%%-Gd)192 or G6E-(%%%1B4M%%%-Gd)256 using a 1.5-T superconductive MRI unit. Although numerous fine vessels of apprx100 mum diameter were visualized on subtracted 3D-MR-angiography with both G6A-(%%%1B4M%%%-Gd)192 and G6E-(%%%1B4M%%%-Gd)256, 153Gd-labeled saturated G6E-(%%%1B4M%%%)256 remained in the blood significantly more than 153Gd-labeled saturated G6A-(%%%1B4M%%%)192 at later than 15 min postinjection ($p < 0.01$). In addition, G6E-(%%%1B4M%%%-Gd)256 visualized these finer vessels longer than G6A-(%%%1B4M%%%-Gd)192. The G6A-(%%%1B4M%%%-Gd)192 showed higher signal intensity in the kidney on the dynamic MR images and brighter kidney images than G6E-(%%%1B4M%%%-Gd)256. In conclusion, the G6A-(%%%1B4M%%%-Gd)192 was observed to go through glomerular filtration more efficiently than G6E-(%%%1B4M%%%-Gd)256 resulting faster clearance from the blood and higher renal accumulation, even though both of G6-%%%1B4M%%% conjugates have almost similar molecular size and same chemical structure. In terms of the ability of intravascular contrast agents, G6E-(%%%1B4M%%%-Gd)256 was better due to more Gd(III) atoms per molecule and longer retention in the circulation than G6A-(%%%1B4M%%%-Gd)192.

? t s17/7/1-9

17/7/1

DIALOG(R)File 5:Biosis Previews(R)

18244097 BIOSIS NO.: 200500151162

Ventilation-synchronous magnetic resonance microscopy of pulmonary structure and ventilation in mice

AUTHOR: Chen Ben T; Yordanov Alexander T; Johnson G Allan (Reprint)

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LANGUAGE: English

ABSTRACT: Increasing use of transgenic animal models for pulmonary disease has raised the need for methods to assess pulmonary structure and function in a physiologically stable mouse. We report here an integrated protocol using magnetic resonance microscopy with %%%gadolinium%%% (Gd)-labeled starburst dendrimer (G6-%%%1B4M%%%-Gd, MW = 192 1 kDa, Rh = 5.50 0.04 nm) and hyperpolarized 3 helium (3He) gas to acquire images that demonstrate pulmonary vasculature and ventilated airways in live mice (n = 9). Registered three-dimensional images of1 H and3 He were acquired during breath-hold at 2.0 T using radial acquisition (total acquisition time of 38 and 25 min, respectively). The macromolecular Gd-labeled dendrimer (a half-life of apprx80 min) increased the signal-to-noise by 81 30% in the left ventricle, 43 22% in the lung periphery, and -4 5% in the chest wall, thus increasing the contrast of these structures relative to the less vascular surrounding

tissues. A constant-flow ventilator was developed for the mouse to deliver varied gas mixtures of O2 and N2 (or3 He) during imaging. To avoid hypoxemia, instrumental dead space was minimized and corrections were made to tidal volume lost due to gas compression. The stability of the physiologic support was assessed by the lack of spontaneous breathing and maintenance of a constant heart rate. We were able to stabilize the mouse for >8 hr using ventilation of 105 breath/min and apprx0.2 mL/breath. The feasibility of acquiring both pulmonary vasculature and ventilated airways was demonstrated in the mouse lung with inplane spatial resolution of 70 x 70 mum2 and slice thickness of 800 mum.

17/7/2
DIALOG(R)File 5:Biosis Previews(R)

17916238 BIOSIS NO.: 200400286995
Functional Pulmonary MR Microscopy in Mice
AUTHOR: Chen Ben T (Reprint); Yordanov Alexander T; Johnson G A
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JOURNAL: FASEB Journal 18 (4-5): pAbst. 538.8 2004 2004
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome Washington, District of Columbia, USA April 17-21, 2004; 20040417
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mouse has become a key animal model to connect genotype to both structural and functional phenotype. As research in functional genomics progresses, the interest in non-invasive assessment of changes in pulmonary structure and function in a physiological stable mouse has

increased. We report here the use of magnetic resonance microscopy with %%%gadolinium%%% (Gd) labeled PAMAM starburst dendrimer and hyperpolarized 3Helium (He) gas to acquire pulmonary images in vivo, indicating perfusion and ventilation distribution in the lung. The images (256x256 with 18 mm field of view) were acquired during breath-hold at 2.0 T using a ventilator-gated 3-dimensional radial encoding technique for thin slices (800 (m). A custom-made constant flow ventilator was used to deliver gas mixtures of 23% O2 and 77% N2 during 1H imaging, and 23% O2 and 77% HP 3He during 3He imaging. To avoid hypoxemia, instrumental dead space was minimized and air compression was corrected for tidal volume. Prior to imaging, the Gd-labeled generation-6 dendrimer (G6-%%%1B4M%%%-Gd, MW = 192(1 kDa, Rh = 5.50(0.04 nm) was administered (160 (g in 0.1 ml) via a tail vein as an intravascular contrast agent (half-life of 80 min). We successfully maintained the mouse at a stable condition throughout the study (>6 hours) using ventilation rate of 105 breaths/min and tidal volume of 0.2 ml. The perfusion and ventilation distributions were demonstrated in the 1H (A) and 3He (B) images with in-plane spatial resolution of 70x70 (m 2. Our results demonstrate the feasibility of perfusion and ventilation distribution in the lung using these techniques. The regional distribution can be assessed, which can provide quantitative comparison of pulmonary disease models. This project is supported by NHLBI R01 HL 055348, NCI R24 CA92656, and NCRR P41 RR05959.

17/7/3

DIALOG(R)File 5:Biosis Previews(R)

16816283 BIOSIS NO.: 200200409794

Dynamic micro-MRI of the micro-circulation in the tumor xenografts using the various sizes of dendrimer-based macromolecular MR contrast agents to evaluate the vascular anatomy and physiology

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Proceedings of the American Association for Cancer Research Annual

Meeting 43 p896 March, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406
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RECORD TYPE: Citation
LANGUAGE: English

17/7/4
DIALOG(R)File 5:Biosis Previews(R)

16428848 BIOSIS NO.: 200200022359
Synthesis and pharmacokinetics of a novel tumor-targeting and internalizing therapeutic agent, avidin-dendrimer-1B4Mx, to deliver radiometals emitting auger electrons into the cell
AUTHOR: Kobayashi H (Reprint); Saga T; Kawamoto S; Sato N; Ishimori T; Haque T L; Mamede M H; Konishi J; Togashi K; Brechbiel M W
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JOURNAL: Journal of Nuclear Medicine 42 (5 Supplement): p258P-259P May, 2001 2001
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CONFERENCE/MEETING: 48th Annual Meeting of the Society of Nuclear Medicine Toronto, Ontario, Canada June 23-27, 2001; 20010623
ISSN: 0161-5505
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RECORD TYPE: Citation
LANGUAGE: English

17/7/5
DIALOG(R)File 5:Biosis Previews(R)

16339448 BIOSIS NO.: 200100511287

Novel liver macromolecular MR contrast agent with a polypropylenimine diaminobutyl dendrimer core: Comparison to the vascular MR contrast agent with the polyamidoamine dendrimer core

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Akita Yukio; Mamede Marcelo H; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Magnetic Resonance in Medicine 46 (4): p795-802 October, 2001

2001

MEDIUM: print

ISSN: 0740-3194

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: As MRI contrast agents, more hydrophobic molecules reportedly accumulate in the liver and thus are potentially useful as liver MRI contrast agents. In this study, a generation-4 polypropylenimine diaminobutane dendrimer (DAB-Am64), which is expected to be more hydrophobic than the generation-4 polyamidoamine dendrimer (PAMAM-G4D), was used to synthesize a conjugate with 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%) (DAB-Am64-(%%%1B4M%%%-Gd)64) for complexing Gd(III) ions. This DAB conjugate quickly accumulated in the liver and its characteristics were studied and compared with those of a PAMAM conjugate (PAMAM-G4D-(%%%1B4M%%%-Gd)64), which is known to be a useful vascular MRI contrast agent, in regard to its availability as a liver MRI contrast agent. DAB-Am64-(%%%1B4M%%%-Gd)64 accumulated significantly more in the liver and less in blood than PAMAM-G4D-(%%%1B4M%%%-Gd)64 ($P<0.001$). Contrast-enhanced MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance liver parenchyma and visualize both portal and hepatic veins of 0.5 mm diameter in mice. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a good candidate for a liver MRI contrast agent.

17/7/6

DIALOG(R)File 5:Biosis Previews(R)

16294816 BIOSIS NO.: 200100466655

Novel intravascular macromolecular MRI contrast agent with generation-4 polyamidoamine dendrimer core: Accelerated renal excretion with coinjection of lysine

AUTHOR: Kobayashi Hisataka (Reprint); Sato Noriko; Kawamoto Satomi; Saga Tsuneo; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Magnetic Resonance in Medicine 46 (3): p457-464 September, 2001 2001

MEDIUM: print

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LANGUAGE: English

ABSTRACT: One of the major limitations to macromolecular MRI contrast agents (MRI-CAs) is their slow clearance and associated decreased excretion of %%%gadolinium%%% (Gd(III)). The effect of coinjecting lysine to accelerate renal excretion of a macromolecular MRI-CA (generation-4 PAMAMTM dendrimer (G4D-(%%%1B4M%%%-Gd)64)) was investigated. The biodistribution and urine and fecal excretion in athymic mice was evaluated with and without lysine coinjection. 3D-dynamic-micro-MRI with G4D-(%%%1B4M%%%-Gd)64 was obtained with and without lysine coinjection, and the serial signal intensity (SI) change in the blood and organs was evaluated. When lysine was coinjected, urinary excretion of G4D-(%%%1B4M%%%-Gd)64 increased 5.4-fold compared to that without lysine, resulting in decreased renal accumulation of G4D-(%%%1B4M%%%-Gd)64 from 150% to 40% injected dose per gram ($P < 0.001$). On dynamic MRI with G4D-(

%%%1B4M%%%-Gd)64, when lysine was coinjected, the kidney-to-blood SI ratio was significantly lower than that obtained without lysine (P < 0.001). When lysine was coinjected, the G4D-(%%%1B4M%%%-Gd)64 was excreted from the kidney intact.

17/7/7

DIALOG(R)File 5:Biosis Previews(R)

16263615 BIOSIS NO.: 200100435454

Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent of %%%gadolinium%%% neutron capture therapy for intraperitoneal disseminated tumor, which can be monitored by MRI

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Ishimori Takayoshi; Tabassum Haque L; Ono Koji; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Graduate School of Medicine, Kyoto University, Kyoto, Japan **Japan

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p382 March, 2001 2001

MEDIUM: print

CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324

SPONSOR: American Association for Cancer Research

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LANGUAGE: English

17/7/8

DIALOG(R)File 5:Biosis Previews(R)

16230692 BIOSIS NO.: 200100402531

Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent

for %%%gadolinium%%% neutron capture therapy of intraperitoneal disseminated tumor which can be monitored by MRI

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Ishimori Takayoshi; Konishi Junji; Ono Koji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Bioconjugate Chemistry 12 (4): p587-593 July-August, 2001 2001

MEDIUM: print

ISSN: 1043-1802

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LANGUAGE: English

ABSTRACT: Peritoneal carcinomatosis is a late stage in cancer progress, for which no effective therapeutic modality exists. Targeting therapeutic agents to disseminated lesions may be a promising modality for treating peritoneal carcinomatosis. %%%Gadolinium%%% (157,155Gd) is known to generate Auger and internal conversion electrons efficiently by irradiation with a neutron beam. Auger electrons from neutron-activated Gd(III) are strongly cytotoxic, but only when Gd(III) atoms have been internalized into the cells. In the present investigation, we have developed a quickly internalizing tumor-targeting system to deliver large quantities of Gd(III) atoms into tumor cells to generate the Auger emission with an external neutron beam. Simultaneously, one would be able to image its biodistribution by MRI with a shortened T1 relaxation time. Avidin-G6-(%%%1B4M%%%-Gd)254 (Av-G6Gd) was synthesized from generation-6 polyamidoamine dendrimer, biotin, avidin, and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%). The Av-G6Gd was radiolabeled with Gd(III) doped with 153Gd. All of the %%%1B4M%%%'s on the conjugate were fully saturated with Gd(III) atoms. An in vitro internalization study showed that Av-G6Gd accumulated and was internalized into SHIN3 cells (a human ovarian cancer) 50- and 3.5-fold greater than Gd-DTPA (Magnevist) and G6-(%%%1B4M%%%-Gd)256 (G6Gd). In addition, accumulation of Gd(III) in the cells was detected by the increased signal on T1-weighted MRI. A

biodistribution study was performed in nude mice bearing intraperitoneally disseminated SHIN3 tumors. Av-G6Gd showed specific accumulation in the SHIN3 tumor (103% ID/g) 366- and 3.4-fold greater than Gd-DTPA (0.28% ID/g, p<0.001) and G6Gd (30% ID/g, p<0.001) 1 day after i.p. injection. Seventy-eight percent of the tumor-related radioactivity of Av-G6Gd in the SHIN3 tumor was located inside the cells. The SHIN3 tumor-to-normal tissue ratio was greater than 17:1 in all organs and increased up to 638:1 at 1 day after i.p. injection. In conclusion, a sufficient amount (162 ppm) of Av-G6Gd was accumulated and internalized into the SHIN3 cells both in vitro and in vivo to kill the cell using 157/155Gd with external irradiation with an appropriate neutron beam while monitoring with MRI. Thus, Av-G6Gd may be a promising agent for Gd neutron capture therapy of peritoneal carcinomatosis. This reagent also has the potential to permit monitoring of its pharmacokinetic progress with MRI.

17/7/9

16180642 BIOSIS NO.: 200100352481

Dynamic micro-magnetic resonance imaging of liver micrometastasis in mice with a novel liver macromolecular magnetic resonance contrast agent DAB-Am64-(%%%1B4M%%%-Gd)64

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

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JOURNAL: Cancer Research 61 (13): p4966-4970 July 1, 2001 2001
MEDIUM: print
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: DAB-Am64-(%%%1B4M%%%-Gd)64 is a newly synthesized macromolecular liver magnetic resonance imaging (MRI) contrast agent with a polypropylenimine diaminobutane (DAB) dendrimer conjugated with a bifunctional diethylenetriaminepentaacetic acid (DTPA) derivative for complexing Gd(III) atoms. The characteristics of DAB-Am64-(%%%1B4M%%%-Gd)64, which quickly accumulated in the liver, have been reported recently. In the present study, the dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was obtained in the mouse liver metastasis model using colon carcinoma cells to evaluate the ability to visualize the micrometastatic tumors compared with that using Gd-DTPA. The dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance the normal liver parenchyma and visualize micrometastatic tumors of 0.3-mm diameter in the liver of the mice with better contrast than that with Gd-DTPA. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a new liver MRI contrast agent potentially useful for diagnosis of micrometastasis in the liver.

? t s20/7/1-7

20/7/1

DIALOG(R)File 5:Biosis Previews(R)

16757747 BIOSIS NO.: 200200351258

Position paper: Need for a cooperative study: Pulmonary Langerhans cell histiocytosis and its management in adults

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JOURNAL: Medical and Pediatric Oncology 39 (1): p35-39 July, 2002 2002

MEDIUM: print

ISSN: 0098-1532

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Pulmonary involvement with Langerhans cell histiocytosis (LCH, formerly known as histiocytosis-X) presents as an %%%interstitial%%% process in children and adults either with or without symptoms. In %%%contrast%%% to other manifestations of LCH, most patients with pulmonary disease are adults. Procedures: We reviewed the literature on pulmonary LCH to determine what were the clinical presentations, prognostic variables, and treatment options for this disease. Results: Although there are spontaneous remissions, a large number of patients have progressive pulmonary deficiency and experience significant morbidity if not mortality from the disease. The efficacy of steroid versus chemotherapy in halting the process remains controversial, even if smoking is taken into consideration. Conclusions: A multicenter study of therapy for pulmonary LCH is the obvious answer to this dilemma. We propose that interested centers organize via the Histiocyte Society to plan and execute such a trial.

20/7/2
DIALOG(R)File 5:Biosis Previews(R)

16295057 BIOSIS NO.: 200100466896
Lung involvement and enzyme replacement therapy in Gaucher's disease
AUTHOR: Goitein O; Elstein D (Reprint); Abrahamov A; Hadas-Halpern I; Melzer E; Kerem E; Zimran A
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JOURNAL: QJM 94 (8): p407-415 August, 2001 2001
MEDIUM: print
ISSN: 1460-2725
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Symptomatic lung involvement in Gaucher's disease is relatively rare, being restricted to patients with other severe manifestations. We describe our experience in eight of 411 patients in our referral clinic, who presented with prominent pulmonary signs or symptoms. There were four adults and four children; all have been successfully treated with enzyme replacement therapy. Routine means of monitoring pulmonary status including clinical assessment, chest %%%X%%%-%%%ray%%%, pulmonary function tests, and high-resolution CT (HRCT) were used. Enzyme treatment resulted in decreased hepatosplenomegaly, improved haematological parameters, and increased well-being; There was decreased clubbing and decreased dyspnoea in some of the patients, although on radiology, lung pathology had not normalized. All four children showed improved respiratory compliance, with significant improvement of the radiological findings in one and unchanged disease in the others. Two adults showed improvement in oxygen saturation but worsening of pulmonary hypertension. On chest %%%X%%%-%%%ray%%%, both had increased %%%interstitial%%% markings; one had gradual progression of pulmonary artery accentuation and fine %%%interstitial%%% stable pattern on HRCT. The other two adults had no change in lung function or on chest %%%X%%%-%%%ray%%%, but on HRCT there was apparent improvement in one patient. There is great heterogeneity in presentation and response to enzyme therapy in patients with Gaucher's disease and symptomatic lung involvement. Clinically, some benefited significantly from enzyme therapy, but in %%%contrast%%% to the dramatic reduction in organomegaly, there was no normalization in pulmonary function or lung architecture.

20/7/3

16134883 BIOSIS NO.: 200100306722

Delayed development of pulmonary toxicity syndrome following busulfan preparative therapy for allogeneic marrow transplantation

AUTHOR: Copelan Edward A (Reprint); Mrozek Ewa (Reprint); Penza Sam L (Reprint); Elder Patrick J (Reprint); Farag Sherif S (Reprint); Marcucci

Guido (Reprint); Bechtel Thomas P; Avalos Belinda R (Reprint)
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JOURNAL: Blood 96 (11 Part 2): p346b November 16, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000; 20001201
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pulmonary toxicity syndrome (PTS) is a progressive (untreated), potentially lethal syndrome of cough, dyspnea, and fever with or without pulmonary infiltrates described in up to 60% of patients within 3 months of autotransplantation with high dose BCNU. It is characterized by a substantial decline in diffusing capacity by pulmonary function testing. We observed this syndrome in 3 of 50 consecutive allogeneic (2 sibling, 1 matched unrelated donor) transplant recipients who underwent transplantation between 6/98 and 8/99. Two patients had CML and one CLL. Preparation for transplant was busulfan and cyclophosphamide with (n=1) or without (n=2) etoposide. Affected patients were males aged 29, 45, and 52. The syndrome occurred more than 5 months, 12 months, and 17 months after transplantation, and in conjunction with tapering (to very low dose) or completed taper of cyclosporine/tacrolimus with or without corticosteroids which had been used in each to treat mild or moderate chronic graft-vs-host disease (GVHD). No patient developed a flare of GVHD in conjunction with PTS or thereafter. All patients reported fatigue, fever, cough, and dyspnea; 2 had diffuse pulmonary infiltrates on chest %%%x%%%-%%%ray%%%, 1 did not and had a normal high resolution chest CT scan. Diffusing capacity dropped by 28%, 49%, and 50% from pretransplant baseline. Bronchoalveolar lavage (BAL) showed 22%, 23%, and 78% neutrophils with negative BAL cultures and no other evidence of infection. In %%%contrast%%% to patients at our institution who developed %%%interstitial%%% pneumonitis within 100 days of allotransplant, where

16/19 patients (over a 4 year period) with BALs showing >10% PMNs died, all 3 of these patients responded to corticosteroid treatment with rapid resolution of symptoms and near correction of their abnormal diffusing capacity. The pulmonary toxicity syndrome, well recognized following autotransplantation with BCNU, is reported here at prolonged intervals from allogeneic transplantation with busulfan. It was associated with tapering to low doses or completed taper of immunosuppression for treatment of chronic GVHD and was not associated with GVHD flare. Prolonged immunosuppression may play a role in the delayed occurrence of this syndrome. It is vital to recognize this variant of idiopathic pneumonia syndrome in that it responds rapidly to corticosteroids but would likely progress without intervention.

20/7/4

16133325 BIOSIS NO.: 200100305164

A case of AIDS in an SC patient: A cautionary tale

AUTHOR: Lawrence Christine; Nagel Ronald L

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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report an illustrative case of a patient with SC disease and AIDS due to HIV 1. A 35 year old woman was hospitalized after two weeks of fever and increasing shortness of breath and pleuritic chest pain. There had been no transfusions, drug abuse, or jaundice. Denies transfusions, drug abuse, hemoglobinopathies or AIDS. At admission she was tachycardic and tachypneic, and her chest %%%x%%%-%%%ray%%% revealed

bilateral lower lobe %%%interstitial%%% infiltrates. A %%%contrast%%%-CT scan showed bilateral pulmonary ground glass infiltrates, a small calcified spleen and no signs of pulmonary infarction. Blood/sputum cultures were negative and she was started on intravenous antibiotics. WBC values: Hb 10.2 g/dl, MCV 79.2 fl, MCHC RDW 17.1; Plt 390k/ul and arterial blood pO2 of 62 mmHg. Blood smear revealed many "billiard ball" and target cells and an unusually high number of typical extra and intra-erythrocytic hemoglobin C-like crystals (40 per 1000) Diagnosis of SC disease was made and confirmed by electrophoresis. Acute chest syndrome was diagnosed because of SC disease, hypoxia, basal infiltrates, decline in her hemoglobin to 7.0 g/dl, decreasing platelets to 287/ul, and lack of response to antibiotics: she was transfused 3 units of packed red cells. IgM Parvovirus B-19 titer was negative. On day 6 broncho-alveolar lavage revealed cysts of the organism and P. carinii pneumonia was diagnosed. She then admitted to her positive HIV status for four years (CD4=17/ul and viral load of 8276 copies per ml). After Bactrim/corticosteroids her dyspnea and chest %%%x%%%-%%%ray%%% abnormalities improved rapidly. We conclude that specialists in infectious diseases and in hematology should be aware that this disease interaction that creates novel diagnostic/%%%therapeutic%%% challenges. PCP pulmonary involvement can induce or coexist with an Acute Chest Syndrome in patients with sickle hemoglobinopathies. The appropriate treatment requires the aggressive use of standard treatment for PCP, and the use of transfusion and/or exchange transfusion to deal with the life-threatening sequestration of sickle red cells in the lung.

15452557 BIOSIS NO.: 200000170870
Spectrum of renal osteodystrophy in children on continuous ambulatory peritoneal dialysis
AUTHOR: Yalcinkaya Fatos (Reprint); Ince Erdal; Tumer Necmiye; Ensari Arzu; Ozkaya Nuray
AUTHOR ADDRESS: Umitkoy, Cinar Sitesi 5.Blok No:62, 06530, Ankara, Turkey**

Turkey
JOURNAL: Pediatrics International 42 (1): p53-57 Feb., 2000 2000
MEDIUM: print
ISSN: 1328-8067
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: The prevalence of different types of bone disease in chronic renal failure (CRF) has changed significantly during the last decade. The aim of the present study is to evaluate the spectrum of bone disease in children with CRF undergoing continuous ambulatory peritoneal dialysis (CAPD). Methods: Seventeen children with CRF on CAPD aged 7-20 years were evaluated. All patients had received regular vitamin D and calcium carbonate therapy during the 6 months preceding the bone biopsy. Serum calcium, phosphate, alkaline phosphatase and immunoreactive parathyroid hormone (iPTH) levels were measured and hand X-rays were performed. Transiliac bone biopsies were analyzed for histologic diagnosis. Results: High turnover renal osteodystrophy (ROD) was the most common bone disease, present in eight patients (47%). Five patients (29%) had low turnover bone disease, and four (24%) had mixed ROD. The mean age of the high turnover ROD group was higher than that of the low turnover group (14 + 3 vs. 11 + 3 years, $P < 0.05$). Seven of the nine patients who had tubulo-%%%interstitial%%% nephritis were found to have high turnover bone disease. In %%%contrast%%%, none of the patients with glomerulonephritis exhibited high turnover bone lesions. Mean serum calcium levels were found to be significantly higher in the low turnover group compared with the patients with high turnover bone disease ($P < 0.001$). A serum iPTH level > 200 pg/mL was 100% sensitive and 66% specific in identifying patients with high turnover ROD. Conclusion: The spectrum of bone disease of the children with CRF undergoing CAPD seems to depend on the rate of CRF and primary disease. The risk of developing overt hyperparathyroid bone disease is high in children with slowly progressing forms of renal pathology and especially in those with tubulo-%%%interstitial%%% disease. In %%%contrast%%%, children with glomerular diseases who had a more rapidly progressive course may have a lesser risk of developing high turnover bone disease. The results of the present

study indicate that even routinely prescribed regular vitamin D therapy early in the course of disease may lead to low turnover bone lesion in small children who have CRF due to rapidly progressive forms of renal pathology.

20/7/6

DIALOG(R)File 5:Biosis Previews(R)

15380523 BIOSIS NO.: 200000098836

Serum marker KL-6/MUC1 for the diagnosis and management of %%%interstitial%%% pneumonitis

AUTHOR: Kohno Nobuoki (Reprint)

AUTHOR ADDRESS: Second Department of Internal Medicine, Ehime University School of Medicine, Onsen-gun, Ehime, 791-0295, Japan**Japan

JOURNAL: Journal of Medical Investigation 46 (3-4): p151-158 Aug., 1999

1999

MEDIUM: print

ISSN: 1343-1420

DOCUMENT TYPE: Article; Literature Review

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: %%%Interstitial%%% pneumonitis includes more than a hundred diseases in which alveolitis is the main manifestation of the affected lung. Symptoms such as dry cough and exertional dyspnea, fine crackles on chest auscultation, %%%interstitial%%% infiltrates on chest %%%X%%%-%%%ray%%% films and CT scans, respiratory function tests, and Ga-67 scintigraphy have been used for the diagnosis and the evaluation of disease activity. However, the poor prognosis of some types of %%%interstitial%%% pneumonitis has not been improved. We discovered a high molecular weight mucin-like antigen, designated KL-6, which is also known as MUC1. The serum level of KL-6/MUC1 was elevated in 70-100% of patients with %%%interstitial%%% pneumonitis, such as pulmonary fibrosis (either idiopathic or related to collagen-vascular disorders), hypersensitivity pneumonitis, sarcoidosis, and radiation pneumonitis. The

levels were significantly higher in patients with active disease than in those with inactive disease. In %%%contrast%%%, patients with noninterstitial lung disease did not show a significant elevation of KL-6/MUC1. Furthermore, the serum KL-6/MUC1 level was found to be an early predictive marker of the %%%therapeutic%%% effect of high-dose corticosteroids in patients with rapidly progressing idiopathic pulmonary fibrosis. These results indicate that KL-6/MUC1 may be a useful serum marker for the diagnosis and monitoring of patients with %%%interstitial%%% pneumonitis.

20/7/7

11889400 BIOSIS NO.: 199396053816

Radiotherapy for the vulvar cancer

AUTHOR: Hirota Saeko (Reprint); Soejima Toshinori (Reprint); Motohara Tomofumi (Reprint); Mieda Chieko (Reprint); Suematsu Tohru (Reprint); Obayashi Kayoko (Reprint); Takada Yoshiki (Reprint); Yoshida Shoji (Reprint); Hasegawa Kazuo
AUTHOR ADDRESS: Dep. Radiol., Hyogo Med. Center Adults, Japan**Japan

JOURNAL: Nippon Acta Radiologica 53 (3): p308-314 1993
ISSN: 0048-0428
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Japanese

ABSTRACT: Fifteen patients who had primary vulvar cancer treated with radiotherapy as an initial treatment at Hyogo Medical Center for Adults and Hyogo Cancer Center from January 1971 to December 1990 are presented. Two patients were stage 0, one stage I, three stage II and nine stage III. Nine patients received electron irradiation with or without %%%interstitial%%% irradiation and intracavitary vaginal irradiation. Five patients received megavoltage %%%X%%%-%%%ray%%% irradiation using AP/PA parallel opposed fields including the pelvic nodes and perineum followed by boost irradiation of electrons, %%%interstitial%%%

irradiation and intracavitary vaginal irradiation. The total dose delivered to the primary tumor ranged from 50 to 100 Gy (73 Gy on average). The actuarial 5-year survival rate of the patients was 43.6%. Complete regression (CR) was achieved in 60% of the patients. However, CT was not achieved in any of five patients with palpable inguinal nodes. In %%%contrast%%%, all the patients who had tumors of less than 2 cm in diameter achieved CR. Five of nine CR cases relapsed. First sites of failure were vagina, groin and vulvar region. Recurrence occurred more than four years after treatment in three cases. Necrosis occurred in five of nine CR cases.

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DIALOG(R)File 5:Biosis Previews(R)

18244097 BIOSIS NO.: 200500151162

Ventilation-synchronous magnetic resonance microscopy of pulmonary structure and ventilation in mice

AUTHOR: Chen Ben T; Yordanov Alexander T; Johnson G Allan (Reprint)

AUTHOR ADDRESS: Med CtrCtr Vivo Microscopy, Duke Univ, Box 3302, Durham, NC, 27710, USA**USA

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JOURNAL: Magnetic Resonance in Medicine 53 (1): p69-75 January 2005 2005

MEDIUM: print

ISSN: 0740-3194 _(ISSN print)

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Increasing use of transgenic animal models for pulmonary disease has raised the need for methods to assess pulmonary structure and function in a physiologically stable mouse. We report here an integrated protocol using magnetic resonance microscopy with %%%gadolinium%%% (Gd)-labeled starburst dendrimer (G6-%%%1B4M%%%-Gd, MW = 192 1 kDa, Rh = 5.50 0.04 nm) and hyperpolarized 3 helium (3He) gas to acquire images that demonstrate pulmonary vasculature and ventilated airways in live mice (n = 9). Registered three-dimensional images of1 H and3 He were acquired during breath-hold at 2.0 T using radial acquisition (total acquisition time of 38 and 25 min, respectively). The macromolecular Gd-labeled dendrimer (a half-life of apprx80 min) increased the signal-to-noise by 81 30% in the left ventricle, 43 22% in the lung periphery, and -4 5% in the chest wall, thus increasing the contrast of these structures relative to the less vascular surrounding tissues. A constant-flow ventilator was developed for the mouse to deliver varied gas mixtures of O2 and N2 (or3 He) during imaging. To avoid hypoxemia, instrumental dead space was minimized and corrections were made to tidal volume lost due to gas compression. The stability of the physiologic support was assessed by the lack of spontaneous breathing and maintenance of a constant heart rate. We were able to stabilize the mouse for >8 hr using ventilation of 105 breath/min and apprx0.2 mL/breath. The feasibility of acquiring both pulmonary vasculature and ventilated airways was demonstrated in the mouse lung with inplane spatial resolution of 70 x 70 mum2 and slice thickness of 800 mum.

17916238 BIOSIS NO.: 200400286995
Functional Pulmonary MR Microscopy in Mice
AUTHOR: Chen Ben T (Reprint); Yordanov Alexander T; Johnson G A
AUTHOR ADDRESS: Center for In Vivo Microscopy, Duke University Medical Center, DUMC Box 3302, Durham, NC, 27710, USA**USA
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JOURNAL: FASEB Journal 18 (4-5): pAbst. 538.8 2004 2004
MEDIUM: e-file
CONFERENCE/MEETING: FASEB Meeting on Experimental Biology: Translating the Genome Washington, District of Columbia, USA April 17-21, 2004; 20040417
SPONSOR: FASEB
ISSN: 0892-6638 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mouse has become a key animal model to connect genotype to both structural and functional phenotype. As research in functional genomics progresses, the interest in non-invasive assessment of changes in pulmonary structure and function in a physiological stable mouse has increased. We report here the use of magnetic resonance microscopy with %%%gadolinium%%% (Gd) labeled PAMAM starburst dendrimer and hyperpolarized 3Helium (He) gas to acquire pulmonary images in vivo, indicating perfusion and ventilation distribution in the lung. The images (256x256 with 18 mm field of view) were acquired during breath-hold at 2.0 T using a ventilator-gated 3-dimensional radial encoding technique for thin slices (800 (m). A custom-made constant flow ventilator was used to deliver gas mixtures of 23% O2 and 77% N2 during 1H imaging, and 23% O2 and 77% HP 3He during 3He imaging. To avoid hypoxemia, instrumental dead space was minimized and air compression was corrected for tidal volume. Prior to imaging, the Gd-labeled generation-6 dendrimer (G6-%%%1B4M%%%-Gd, MW = 192(1 kDa, Rh = 5.50(0.04 nm) was administered (160 (g in 0.1 ml) via a tail vein as an intravascular contrast agent (half-life of 80 min). We successfully maintained the mouse at a stable condition throughout the study (>6 hours) using ventilation rate of 105 breaths/min and tidal volume of 0.2 ml. The perfusion and ventilation distributions were demonstrated in the 1H (A) and 3He (B) images with in-plane spatial resolution of 70x70 (m 2. Our results demonstrate the feasibility of perfusion and ventilation distribution in the lung using these techniques. The regional distribution can be assessed, which can provide quantitative comparison of pulmonary disease models. This project is supported by NHLBI R01 HL 055348, NCI R24 CA92656, and NCRR P41 RR05959.

2/7/3

DIALOG(R)File 5:Biosis Previews(R)

16816283 BIOSIS NO.: 200200409794

Dynamic micro-MRI of the micro-circulation in the tumor xenografts using the various sizes of dendrimer-based macromolecular MR contrast agents to evaluate the vascular anatomy and physiology

AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: NCI, NIH, Bethesda, MD, USA**USA

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p896 March, 2002 2002

MEDIUM: print

CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406

ISSN: 0197-016X

DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Citation

LANGUAGE: English

2/7/4

DIALOG(R)File 5:Biosis Previews(R)

16428848 BIOSIS NO.: 200200022359

Synthesis and pharmacokinetics of a novel tumor-targeting and internalizing therapeutic agent, avidin-dendrimer-1B4Mx, to deliver radiometals emitting auger electrons into the cell

AUTHOR: Kobayashi H (Reprint); Saga T; Kawamoto S; Sato N; Ishimori T; Haque T L; Mamede M H; Konishi J; Togashi K; Brechbiel M W

AUTHOR ADDRESS: Graduate School of Medicine, Kyoto University, Kyoto, Japan **Japan

JOURNAL: Journal of Nuclear Medicine 42 (5 Supplement): p258P-259P May, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 48th Annual Meeting of the Society of Nuclear Medicine Toronto, Ontario, Canada June 23-27, 2001; 20010623
ISSN: 0161-5505
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/5
DIALOG(R)File 5:Biosis Previews(R)

16339448 BIOSIS NO.: 200100511287
Novel liver macromolecular MR contrast agent with a polypropylenimine diaminobutyl dendrimer core: Comparison to the vascular MR contrast agent with the polyamidoamine dendrimer core
AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Akita Yukio; Mamede Marcelo H; Konishi Junji; Togashi Kaori; Brechbiel Martin W
AUTHOR ADDRESS: Department of Diagnostic and Interventional Imagiology, Graduate School of Medicine, Hitachi Medial Co., Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan
JOURNAL: Magnetic Resonance in Medicine 46 (4): p795-802 October, 2001 2001
MEDIUM: print
ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: As MRI contrast agents, more hydrophobic molecules reportedly accumulate in the liver and thus are potentially useful as liver MRI contrast agents. In this study, a generation-4 polypropylenimine diaminobutane dendrimer (DAB-Am64), which is expected to be more

hydrophobic than the generation-4 polyamidoamine dendrimer (PAMAM-G4D), was used to synthesize a conjugate with 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%) (DAB-Am64-(%%%1B4M%%%-Gd)64) for complexing Gd(III) ions. This DAB conjugate quickly accumulated in the liver and its characteristics were studied and compared with those of a PAMAM conjugate (PAMAM-G4D-(%%%1B4M%%%-Gd)64), which is known to be a useful vascular MRI contrast agent, in regard to its availability as a liver MRI contrast agent. DAB-Am64-(%%%1B4M%%%-Gd)64 accumulated significantly more in the liver and less in blood than PAMAM-G4D-(%%%1B4M%%%-Gd)64 ($P<0.001$). Contrast-enhanced MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance liver parenchyma and visualize both portal and hepatic veins of 0.5 mm diameter in mice. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a good candidate for a liver MRI contrast agent.

2/7/6

16294816 BIOSIS NO.: 200100466655

Novel intravascular macromolecular MRI contrast agent with generation-4 polyamidoamine dendrimer core: Accelerated renal excretion with coinjection of lysine

AUTHOR: Kobayashi Hisataka (Reprint); Sato Noriko; Kawamoto Satomi; Saga Tsuneo; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Hitachi Medical Co. Chaired Department of Diagnostic and Interventional Imaging, Kyoto University, Graduate School of Medicine, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan

JOURNAL: Magnetic Resonance in Medicine 46 (3): p457-464 September, 2001
2001
MEDIUM: print
ISSN: 0740-3194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: One of the major limitations to macromolecular MRI contrast agents (MRI-CAs) is their slow clearance and associated decreased excretion of %%%gadolinium%%% (Gd(III)). The effect of coinjecting lysine to accelerate renal excretion of a macromolecular MRI-CA (generation-4 PAMAMTM dendrimer (G4D-(%%%1B4M%%%-Gd)64)) was investigated. The biodistribution and urine and fecal excretion in athymic mice was evaluated with and without lysine coinjection. 3D-dynamic-micro-MRI with G4D-(%%%1B4M%%%-Gd)64 was obtained with and without lysine coinjection, and the serial signal intensity (SI) change in the blood and organs was evaluated. When lysine was coinjected, urinary excretion of G4D-(%%%1B4M%%%-Gd)64 increased 5.4-fold compared to that without lysine, resulting in decreased renal accumulation of G4D-(%%%1B4M%%%-Gd)64 from 150% to 40% injected dose per gram ($P < 0.001$). On dynamic MRI with G4D-(%%%1B4M%%%-Gd)64, when lysine was coinjected, the kidney-to-blood SI ratio was significantly lower than that obtained without lysine ($P < 0.001$). When lysine was coinjected, the G4D-(%%%1B4M%%%-Gd)64 was excreted from the kidney intact.

2/7/7

16263615 BIOSIS NO.: 200100435454

Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent of %%%gadolinium%%% neutron capture therapy for intraperitoneal disseminated tumor, which can be monitored by MRI

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Ishimori Takayoshi; Tabassum Haque L; Ono Koji; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Graduate School of Medicine, Kyoto University, Kyoto, Japan **Japan

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 42 p382 March, 2001 2001

MEDIUM: print

CONFERENCE/MEETING: 92nd Annual Meeting of the American Association for

Cancer Research New Orleans, LA, USA March 24-28, 2001; 20010324
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/8
DIALOG(R)File 5:Biosis Previews(R)

16230692 BIOSIS NO.: 200100402531
Avidin-dendrimer-(%%%1B4M%%%-Gd)254: A tumor-targeting therapeutic agent for %%%gadolinium%%% neutron capture therapy of intraperitoneal disseminated tumor which can be monitored by MRI
AUTHOR: Kobayashi Hisataka (Reprint); Kawamoto Satomi; Saga Tsuneo; Sato Noriko; Ishimori Takayoshi; Konishi Junji; Ono Koji; Togashi Kaori; Brechbiel Martin W
AUTHOR ADDRESS: Department of Diagnostic and Interventional Imagiology, Graduate School of Medicine, Hitachi Medial Co., Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan
JOURNAL: Bioconjugate Chemistry 12 (4): p587-593 July-August, 2001 2001
MEDIUM: print
ISSN: 1043-1802
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Peritoneal carcinomatosis is a late stage in cancer progress, for which no effective therapeutic modality exists. Targeting therapeutic agents to disseminated lesions may be a promising modality for treating peritoneal carcinomatosis. %%%Gadolinium%%% (157,155Gd) is known to generate Auger and internal conversion electrons efficiently by irradiation with a neutron beam. Auger electrons from neutron-activated Gd(III) are strongly cytotoxic, but only when Gd(III) atoms have been internalized into the cells. In the present investigation, we have

developed a quickly internalizing tumor-targeting system to deliver large quantities of Gd(III) atoms into tumor cells to generate the Auger emission with an external neutron beam. Simultaneously, one would be able to image its biodistribution by MRI with a shortened T1 relaxation time. Avidin-G6-(%%%1B4M%%%-Gd)254 (Av-G6Gd) was synthesized from generation-6 polyamidoamine dendrimer, biotin, avidin, and 2-(p-isothiocyanatobenzyl)-6-methyl-diethylenetriaminepentaacetic acid (%%%1B4M%%%). The Av-G6Gd was radiolabeled with Gd(III) doped with 153Gd. All of the %%%1B4M%%%'s on the conjugate were fully saturated with Gd(III) atoms. An in vitro internalization study showed that Av-G6Gd accumulated and was internalized into SHIN3 cells (a human ovarian cancer) 50- and 3.5-fold greater than Gd-DTPA (Magnevist) and G6-(%%%1B4M%%%-Gd)256 (G6Gd). In addition, accumulation of Gd(III) in the cells was detected by the increased signal on T1-weighted MRI. A biodistribution study was performed in nude mice bearing intraperitoneally disseminated SHIN3 tumors. Av-G6Gd showed specific accumulation in the SHIN3 tumor (103% ID/g) 366- and 3.4-fold greater than Gd-DTPA (0.28% ID/g, $p<0.001$) and G6Gd (30% ID/g, $p<0.001$) 1 day after i.p. injection. Seventy-eight percent of the tumor-related radioactivity of Av-G6Gd in the SHIN3 tumor was located inside the cells. The SHIN3 tumor-to-normal tissue ratio was greater than 17:1 in all organs and increased up to 638:1 at 1 day after i.p. injection. In conclusion, a sufficient amount (162 ppm) of Av-G6Gd was accumulated and internalized into the SHIN3 cells both in vitro and in vivo to kill the cell using 157/155Gd with external irradiation with an appropriate neutron beam while monitoring with MRI. Thus, Av-G6Gd may be a promising agent for Gd neutron capture therapy of peritoneal carcinomatosis. This reagent also has the potential to permit monitoring of its pharmacokinetic progress with MRI.

2/7/9

16180642 BIOSIS NO.: 200100352481

Dynamic micro-magnetic resonance imaging of liver micrometastasis in mice

with a novel liver macromolecular magnetic resonance contrast agent DAB-Am64-(%%%1B4M%%%-Gd)64

AUTHOR: Kobayashi Hisataka (Reprint); Saga Tsuneo; Kawamoto Satomi; Sato Noriko; Hiraga Akira; Ishimori Takayoshi; Konishi Junji; Togashi Kaori; Brechbiel Martin W

AUTHOR ADDRESS: Department of Diagnostic and Interventional Radiology, Graduate School of Medicine, Kyoto University, 54, Kawahara-cho, Shogoin, Sakyo, Kyoto, 606-8507, Japan**Japan

JOURNAL: Cancer Research 61 (13): p4966-4970 July 1, 2001 2001

MEDIUM: print

ISSN: 0008-5472

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: DAB-Am64-(%%%1B4M%%%-Gd)64 is a newly synthesized macromolecular liver magnetic resonance imaging (MRI) contrast agent with a polypropylenimine diaminobutane (DAB) dendrimer conjugated with a bifunctional diethylenetriaminepentaacetic acid (DTPA) derivative for complexing Gd(III) atoms. The characteristics of DAB-Am64-(%%%1B4M%%%-Gd)64, which quickly accumulated in the liver, have been reported recently. In the present study, the dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was obtained in the mouse liver metastasis model using colon carcinoma cells to evaluate the ability to visualize the micrometastatic tumors compared with that using Gd-DTPA. The dynamic micro-MRI with DAB-Am64-(%%%1B4M%%%-Gd)64 was able to homogeneously enhance the normal liver parenchyma and visualize micrometastatic tumors of 0.3-mm diameter in the liver of the mice with better contrast than that with Gd-DTPA. In conclusion, DAB-Am64-(%%%1B4M%%%-Gd)64 is a new liver MRI contrast agent potentially useful for diagnosis of micrometastasis in the liver.

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7/7/1

DIALOG(R)File 5:Biosis Previews(R)

18251934 BIOSIS NO.: 200500158106

Real-time in vivo imaging of the convective distribution of a low-molecular-weight %%%tracer%%%

AUTHOR: Croteau David; Walbridge Stuart; Morrison Paul F; Butman John A; Vortmeyer Alexander O; Johnson Dennis; Oldfield Edward H; Lonser Russell R (Reprint)

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JOURNAL: Journal of Neurosurgery 102 (1): p90-97 January 2005 2005

MEDIUM: print

ISSN: 0022-3085

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Object. Convection-enhanced delivery (CED) is increasingly used to distribute therapeutic agents to locations in the central nervous system. The optimal application of convective distribution of various agents requires the development of imaging tracers to monitor CED in vivo in real time. The authors examined the safety and utility of an iodine-based low-molecular-weight surrogate %%%tracer%%% for computerized tomography (CT) scanning during CED. Methods. Various volumes (total volume range 90-150 mul) of %%%iopamidol%%% (MW 777 D) were delivered to the cerebral white matter of four primates (Macaca mulatta) by using CED. The distribution of this imaging %%%tracer%%% was determined by in vivo real-time and postinfusion CT scanning (Itoreq 5 days after infusion (one animal)) as well as by quantitative autoradiography (14C-sucrose (all animals) and14 C-dextran (one animal)), and compared with a mathematical model. Clinical observation (Itoreq 5 months) and histopathological analyses were used to evaluate the safety and toxicity of the %%%tracer%%% delivery. Real-time CT scanning of the %%%tracer%%% during infusion revealed a clearly definable region of perfusion. The volume of distribution (Vd) increased linearly (r2 = 0.97) with an increasing volume of infusion (Vi). The overall Vd/Vi ratio was 4.1 0.7 (mean

standard deviation) and the distribution of infusate was homogeneous. Quantitative autoradiography confirmed the accuracy of the imaged distribution for a small (sucrose, MW 359 D) and a large (dextran, MW 70 kD) molecule. The distribution of the infusate was identifiable up to 72 hours after infusion. There was no clinical or histopathological evidence of toxicity in any animal. Conclusions. Real-time in vivo CT scanning of CED of %%%iopamidol%%% appears to be safe, feasible, and suitable for monitoring convective delivery of drugs with certain features and low infusion volumes.

7/7/2

DIALOG(R)File 5:Biosis Previews(R)

17862846 BIOSIS NO.: 200400232555

Sentinel lymph node biopsy using computed tomography-lymphography in patients with breast cancer.

AUTHOR: Tangoku Akira (Reprint); Yamamoto Shigeru; Suga Kazuyoshi; Ueda Katsuhiko; Nagashima Yukiko; Hida Makoto; Sato Tomomitsu; Sakamoto Kazuhiko; Oka Masaaki

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JOURNAL: Surgery (St Louis) 135 (3): p258-265 March 2004 2004

MEDIUM: print

ISSN: 0039-6060 _(ISSN print)

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Background. The sentinel lymph node biopsy (SLNB) technique is established in the treatment of breast cancer. The current technique of mapping the SLN with blue dye or radiotracers requires a learning period. %%%Tracer%%% and injection site selection and intraoperative pathologic examination have been discussed. Methods. We developed a three-dimensional computed tomography lymphography (3D CT-LG) technique with commercially available %%%iopamidol%%%. SLNB and backup dissection

were performed in 40 patients with T1 and T2 breast cancer. Feasibility and efficacy of CT-LG were examined. Results. In all patients, lymph flow and the surrounding anatomical environment were visualized with 3D CT-LG. SLNB was successful because of accurate navigation by 3D CT-LG. SLN was detected in all patients, whereas dye navigation failed in seven fatty axilla and two patients with prior excisional biopsy. Backup dissection confirmed the accuracy of CT-LG-guided SLNB. A false negative result was found in only one patient. Preoperative prediction was feasible in cases of SLN metastasis. Conclusions. CT-LG allowed accurate SLN localization by quickly and adequately visualizing the direct connection between the SLN and its afferent lymphatic vessels. Detailed cross-sectional images of lymphatic anatomy during CT resulted in successful SLNB with shortening of the presurgical examination schedule.

7/7/3

08045639 BIOSIS NO.: 198681009530

ABSENCE OF MYOCARDIAL BIOCHEMICAL TOXICITY WITH A NONIONIC CONTRAST AGENT

%%%IOPAMIDOL%%%

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JOURNAL: American Heart Journal 110 (3): p609-617 1985
ISSN: 0002-8703
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: To evaluate the myocardial metabolic effects of a new nonionic contrast agent, %%%iopamidol%%%, a randomized, double-blind study was performed comparing %%%iopamidol%%% with sodium meglumine diatrizoate (Renografin-76) in 23 patients with ischemic heart disease. Coronary

sinus and arterial metabolic samples were obtained prior to and during the 20-minute period following the contrast left ventriculogram. Ten patients received %%%iopamidol%%% and 13 received Renografin-76. The chemical lactate extraction in the %%%iopamidol%%% group was 13 .+. 9% prior to left ventriculography and 17 .+. 12% following the contrast injection ($p < 0.005$). In the Renografin-76 group, the lactate extraction was 23 .+. 13% and decreased significantly to 12 .+. 24% following the ventriculogram ($p < 0.01$). In a subset of these patients ($n = 10$), [1-14C] lactate was infused as a %%%tracer%%% to quantitate the amount of lactate released by the myocardium. [1-14C] lactate analysis demonstrated that the fall in lactate extraction ratio following Renografin-76 was due to an increase in myocardial lactate release. In the Renografin-76 group there was a 53 .+. 37% increase in lactate release at 10 minutes after contrast agent injection ($p < 0.005$), while in the %%%iopamidol%%% patients there was no significant change in lactate release following contrast ventriculography. The increase in lactate release in the Renografin-76 group suggests that myocardial ischemia is induced with this ionic contrast agent. In comparison, the nonionic contrast agent is less toxic to the myocardium and is not associated with the biochemical changes of cellular ischemia.

7/7/4

07800913 BIOSIS NO.: 198580109808

COMPARATIVE NEUROTOXICITY OF ANGIOGRAPHIC CONTRAST MEDIA

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JOURNAL: Neurology 35 (9): p1290-1298 1985
ISSN: 0028-3878
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The neurotoxic effects in cerebral angiography of 3 iodinated ionic contrast media, nonionic %%%iopamidol%%%, 25% mannitol and saline controls were compared in 25 rabbits. Diatrizoate sodium meglumine was the most toxic agent, followed by diatrizoate meglumine, iothalamate meglumine, and mannitol in terms of blood-brain barrier (BBB) disruption and coupled perfusion decline. HIPDm [N,N,N'-trimethyl-N'-[2-hydroxyl-3-methyl-5-iodobenzyl] 1,3,propanediamine I123] distribution was more sensitive than trypan blue extravasation for monitoring brain dysfunction. %%%Iopamidol%%% and saline controls exhibited no visual BBB breakdown or alteration in regional uptake of I-125 HIPDm, confirming the safety of nonionic %%%iopamidol%%% as compared with presently used ionic contrast media.

06960064 BIOSIS NO.: 198376051499
FEMORAL ARTERY FLOW AND PAIN DURING LUMBAR AORTOGRAPHY COMPARISON OF IONIC AND NONIONIC CONTRAST MEDIA
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JOURNAL: Clinical Radiology 34 (1): p79-85 1983
ISSN: 0009-9260
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A method is described for noninvasively measuring the increase in lower limb blood flow during transfemoral lumbar aortography. Flow-measurements were made using a continuous wave Doppler-shift ultrasound transducer placed over the contralateral femoral artery. The effect of the nonionic contrast medium B15000 (%%%Iopamidol%%%),

conventional contrast medium (Urografin 370) and Urografin 370 plus Lignocaine were compared in a double-blind trial. All 3 produced an increase in flow which reached a peak between 12 and 45 s after injection. The peak flow following %%%Iopamidol%%% was significantly lower than that from both Urografin 370 alone and with addition of Lignocaine. There was a difference of lesser degree between Urografin 370 plus Lignocaine and Urografin 370 alone; this was not statistically significant. The subjective assessments of pain and patient discomfort paralleled these objective flow measurements.

? t s9/7/1-21

A16/iopamide

9/7/1

DIALOG(R)File 5:Biosis Previews(R)

18411107 BIOSIS NO.: 200510105607

Electrospray ionization mass spectrometry as a tool for determination of drug binding sites to human serum %%%albumin%%% by noncovalent interaction

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JOURNAL: Rapid Communications in Mass Spectrometry 19 (12): p1637-1643 05 2005

ISSN: 0951-4198

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Most proteins in blood plasma bind ligands. Human serum %%%albumin%%% (HSA) is the main transport protein with a very high capacity for binding of endogenous and exogenous compounds in plasma. Many pharmacokinetic properties of a drug depend on the level of binding to plasma proteins. This work reports studies of noncovalent interactions by means of nanoelectrospray ionization mass spectrometry (nanoESI-MS)

for determination of the specific binding of selected drug candidates to HSA. Warfarin, %%%iopanoic%%% acid and digitoxin were chosen as site-specific probes that bind to the main sites of HSA. Two drug candidates and two known binders to HSA were analyzed using a competitive approach. The drugs were incubated with the target protein followed by addition of site-specific probes, one at a time. The drug candidates showed predominant affinity to site I (warfarin site). Naproxen and glyburide showed affinity to both sites I and II. The advantages of nanoE-SI-MS for these studies are the sensitivity, the absence of labeled molecules and the short method development time.

9/7/2

DIALOG(R)File 5:Biosis Previews(R)

17651306 BIOSIS NO.: 200400018290

Inhibition of drug binding to human serum %%%albumin%%% by cholecystographic agents.

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JOURNAL: Farmaco (Lausanne) 58 (9): p901-908 September 2003 2003

MEDIUM: print

ISSN: 0014-827X

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LANGUAGE: English

ABSTRACT: The binding of two cholecystographic agents to human serum %%%albumin%%% (HSA) was evaluated by means of two different complementary methodologies. In particular, the inhibition of drug HSA binding caused by %%%iopanoic%%%- and iophenoxic-acid was investigated by circular dichroism (CD) and resonant mirror (RM) optical biosensor techniques. The CD study allowed to obtain information both on the cholecystographic

agent binding site and on the effect of the binding on the protein conformation. %%%Iopanoic%%% acid (IOP), a drug potentially useful for thyrotoxic disorders, resulted a direct competitor for ligands that selectively bind to site II, in agreement to literature data. No definite evidence was obtained for the highest affinity binding site of iophenoxic acid (IOPH), however, this diagnostic tool markedly affected the binding of ligands to the most characterized high affinity sites on HSA, namely sites I, II and III. Binding parameters were obtained by optical biosensor analysis: KD values were 3.6X10-7 and 2.8X10-8 M for IOP and IOPH, respectively.

9/7/3

17214523 BIOSIS NO.: 200300173242

Convective distribution of macromolecules in the primate brain demonstrated using computerized tomography and magnetic resonance imaging.

AUTHOR: Nguyen Tung T; Pannu Yashdip S; Sung Cynthia; Dedrick Robert L; Walbridge Stuart; Brechbiel Martin W; Garmestani Kayhan; Beitzel Markus; Yordanov Alexander T; Oldfield Edward H (Reprint)
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JOURNAL: Journal of Neurosurgery 98 (3): p584-590 March 2003 2003
MEDIUM: print
ISSN: 0022-3085
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Object. Convection-enhanced delivery (CED), the delivery and distribution of drugs by the slow bulk movement of fluid in the extracellular space, allows delivery of therapeutic agents to large

volumes of the brain at relatively uniform concentrations. This mode of drug delivery offers great potential for the treatment of many neurological disorders, including brain tumors, neurodegenerative diseases, and seizure disorders. An analysis of the treatment efficacy and toxicity of this approach requires confirmation that the infusion is distributed to the targeted region and that the drug concentrations are in the therapeutic range. Methods. To confirm accurate delivery of therapeutic agents during CED and to monitor the extent of infusion in real time, %%%albumin%%%-linked surrogate tracers that are visible on images obtained using noninvasive techniques (%%%iopanoic%%% acid (IPA) for computerized tomography (CT) and Gd-diethylenetriamine pentaacetic acid for magnetic resonance (MR) imaging) were developed and investigated for their usefulness as surrogate tracers during convective distribution of a macromolecule. The authors infused %%%albumin%%%-linked tracers into the cerebral hemispheres of monkeys and measured the volumes of distribution by using CT and MR imaging. The distribution volumes measured by imaging were compared with tissue volumes measured using quantitative autoradiography with (14C)bovine serum %%%albumin%%% coinfused with the surrogate tracer. For in vivo determination of tracer concentration, the authors examined the correlation between the concentration of the tracer in brain homogenate standards and CT Hounsfield units. They also investigated the long-term effects of the surrogate tracer for CT scanning, IPA-%%%albumin%%%, on animal behavior, the histological characteristics of the tissue, and parenchymal toxicity after cerebral infusion. Conclusions. Distribution of a macromolecule to clinically significant volumes in the brain is possible using convection. The spatial dimensions of the tissue distribution can be accurately defined in vivo during infusion by using surrogate tracers and conventional imaging techniques, and it is expected that it will be possible to determine local concentrations of surrogate tracers in voxels of tissue in vivo by using CT scanning. Use of imaging surrogate tracers is a practical, safe, and essential tool for establishing treatment volumes during high-flow interstitial microinfusion of the central nervous system.

15300020 BIOSIS NO.: 200000018333

%%%Iopanoic%%% acid-induced decrease of circulating T3 causes a significant increase in GH responsiveness to GH releasing hormone in thyrotoxic patients

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JOURNAL: Clinical Endocrinology 51 (4): p461-467 Oct., 1999 1999
MEDIUM: print
ISSN: 0300-0664
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: OBJECTIVE: Thyroid hormones participate in GH synthesis and secretion, and an impaired GH response to many pharmacological stimuli, including GH releasing hormone (GHRH), has been found in thyrotoxicosis. Although the mechanisms involved in this process have not been fully elucidated, there is evidence that thyroid hormones could act at both hypothalamic and pituitary levels. There are no data in the literature about the effect of an acute reduction of circulating T3 levels on GH secretion in hyperthyroidism. The GH responsiveness to GHRH was therefore evaluated in a group of hyperthyroid patients during short-term treatment with %%%iopanoic%%% acid. %%%Iopanoic%%% acid is a compound that induces a rapid decrease in serum T3 levels, mainly by inhibition of peripheral conversion of T4 to T3. To the authors' knowledge, there is no evidence of a direct effect of %%%iopanoic%%% acid on GH secretion. DESIGN: Hyperthyroid patients were submitted to a GHRH test (100 mug, i.v.) before (day 0), and on days 4, 7 and 15 after oral treatment with %%%iopanoic%%% acid (3 g every 3 days) and propylthiouracil (200 mg every 8 h). A group of normal control subjects was also submitted to a single GHRH test (100 mug, i.v.). PATIENTS: Nine patients with thyrotoxicosis (eight women, one man), with a mean age of 34 years, were studied. All patients had high serum levels of total T3 and total T4, and suppressed

TSH levels. None of them had taken any medication for at least 3 months before the study. The patients were compared with a group of nine control subjects (five women, four men) with a mean age of 31 years. MEASUREMENTS: GH and TSH were measured by immunofluorometric assays. Total T3, total T4 and IGF-I were determined by radioimmunoassay. %%%Albumin%%% levels were measured by a colorimetric method. RESULTS: %%%Iopanoic%%% acid induced a rapid and maintained decrease in serum T3 concentrations, with a significant reduction on days 4, 7 and 15 compared with pre-treatment values. In hyperthyroidism, peak GH levels (mean + SE mU/l) after GHRH were significantly higher on day 15 (24.4 + 3.8) than those observed on days 0 (14.2 + 1.6), 4 (15.2 + 3.0) and 7 (19.6 + 5.0). There was a 79% increase in this response on day 15 compared with the pre-treatment period. Hyperthyroid patients had a blunted GH response to GHRH on days 0, 4 and 7 in comparison with control subjects. However, on day 15, no differences were observed between the area under the curve (mean + SE mU/l.120 min) in thyrotoxic patients (1770 + 306) and in the control group (3300 + 816). IGF-I and %%%albumin%%% levels did not change during %%%iopanoic%%% acid administration. CONCLUSIONS: The results show that an acute reduction in serum T3 levels elicits an increase in GH responsiveness to GHRH in hyperthyroidism. Although the mechanisms involved in this process are still unknown, it is possible that T3 influences GH responsiveness to GHRH via hypothalamic somatostatin release. Alternatively, T3 could have a direct effect at the pituitary somatot roph, modulating GHRH intracellular pathways.

9/7/5

10952737 BIOSIS NO.: 199242055628

CRITERION FOR EVALUATING THE INTERACTION OF LIGANDS WITH MACROMOLECULES
FROM HIGH RESOLUTION NMR SPECTROSCOPY

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JOURNAL: Biophysics (English Translation of Biofizika) 33 (5): p835-840 1988
ISSN: 0006-3509
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: ENGLISH

9/7/6
DIALOG(R)File 5:Biosis Previews(R)

10252513 BIOSIS NO.: 199090036992
KINETIC ASSESSMENT OF APPARENT FACILITATION BY %%%ALBUMIN%%% OF CELLULAR
UPTAKE OF UNBOUND LIGANDS
AUTHOR: MORGAN D J (Reprint); STEAD C K; SMALLWOOD R A
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JOURNAL: Journal of Pharmacokinetics and Biopharmaceutics 18 (2): p121-136 1990
ISSN: 0090-466X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Previous studies of the effect of %%%albumin%%% on initial uptake of ligands by isolated cell suspensions or cultures found that the apparent uptake for unbound ligand appeared larger in the presence of binding to the %%%albumin%%% than when %%%albumin%%% was absent. Furthermore, when ligand and %%%albumin%%% were increased in a fixed molar ratio, uptake appeared to be competitively inhibited by the excess %%%albumin%%%. We examined the kinetics underlying this apparent facilitation phenomenon by incorporating unbond fraction of ligand in the medium (fu1) into the general model for diffusion between two

compartments. The analysis showed that even in the absence of facilitation by %%%albumin%%%, the apparent rate constant for uptake of unbound ligand (k/fu1) increases as %%%albumin%%% concentration increases but the uptake clearance of unbound ligand remains constant. This theoretical analysis was verified experimentally by measuring the effect of %%%albumin%%% on uptake rates of 14C-taurocholate (12, 24, 48, 60, and 96 .mu.M, with and without 0.87 mM %%%albumin%%%) in a nonphysiological system consisting of two solutions separated by a cellulose membrane. Moreover, when the taurocholate and %%%albumin%%% concentrations were increased in a fixed molar ratio of 0.06 (taurocholate 12-96 .mu.M, %%%albumin%%% 0.2-1.6 mM), the initial uptake rate exhibited the same nonlinear pattern as the previous studies that used living cells. This pattern was due not to saturation of a putative %%%albumin%%% receptor but simply to the concomitant decrease in fu1 which tended to offset the increase in uptake rate due to the increasing total taurocholate concentration. The model was also used to evaluate published data describing the effect of %%%albumin%%% on the uptake of %%%iopanoic%%% acid by cultured hepatocytes. In accordance with the model, k1/fu1 increased as ablumin concentration increased, but uptake clearance was independent of %%%albumin%%% concentration. Therefore, the kinetic pattern found in this and other studies with isolated cell suspensions or cultures argues against a special role for %%%albumin%%% in faciliating cellular ligand uptake.

9/7/7

09633120 BIOSIS NO.: 198987081011

UPTAKE OF 3 5 3' TRIIODOTHYRONINE BY CULTURED RAT HEPATOMA CELLS IS INHIBITABLE BY NONBILE ACID CHOLEPHILS DIPHENYLHYDANTOIN AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS

AUTHOR: TOPLISS D J (Reprint); KOLLINIATIS E; BARLOW J W; LIM C-F; STOCKIGT J R

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JOURNAL: Endocrinology 124 (2): p980-986 1989
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Cellular uptake of T3 was examined using rat H4 hepatoma cells. Uptake of [125I]T3 (10-11 M) from serum-free medium was measured as the cell-associated counts retained by washed cells (2 .times. 106 per well). Displaceable uptake was 84% of total uptake at 2 min (2.9% of total counts). T4, tetraiodothyroacetic acid, triiodothyroacetic acid, rT3, and D-T3 was 2-5% as effective as T3 in displacing uptake. Nonequilibrium kinetics indicated a half-maximal uptake at 680 nM T3 with approximately 7 million sites per cell. Displaceable uptake was time and temperature dependent and was 73% inhibited by 2 mM KCN and 52% by 10 mM bacitracin but not by 2 mM ouabain or 10 .mu.M cytochalasin B. Phloretin, 100 .mu.M, inhibited uptake by 66%. T3 uptake was directly related to the free T3 concentration over the range of %%%albumin%%% concentrations, 0-10 g/liter. The nonbile acid cholephil compounds, bromosulfophthalein, %%%iopanoic%%% acid, and indocyanine green (all 100 .mu.M) inhibited t3 uptake to 62%, 17%, and 5% of control, respectively. Taurocholate, methylaminoisobutyric acid, and oleic acid were noninhibitory. The half-inhibitory concentrations of reactive nonsteroidal antiinflammatory drugs were: meclofenamic acid (25 .mu.M), mefenamic acid (45 .mu.M), fenclofenac (69 .mu.M), flufenamic acid (100 .mu.M), and diclofenac (230 .mu.m). Aspirin, ibuprofen, oxyphenbutazone, and phenylbutazone (all 100 .mu.M) were noninhibitory. Diphenylhydantoin inhibited uptake to 50% at 75 .mu.M. These findings suggest that T3 uptke by cultured rat hepatocytes is by an energy-dependent, saturable, stereo-selective mechanism that is dependent on cell membrane proteins. This mechanism appears to be shared by a number of other ligands, including nonbile acid cholephils and several nonsteroidal antiinflammatory drugs of the anthranilic and phenylacetic acid classes, as well as diphenylhydantoin. The bile acid taurocholate, oleic acid, and a probe for type A amino acid

uptake were inactive. The extent to which these effects may modify expression of thyroid hormone action remains to be established.

9/7/8

08753075 BIOSIS NO.: 198784107224

THE EFFECT OF %%%IOPANOIC%%% ACID ON THYROTROPIN SECRETION IN PATIENTS WITH
CIRRHOSIS OF THE LIVER

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JOURNAL: Endocrinologia Japonica 34 (4): p531-538 1987
ISSN: 0013-7219
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Ten patients with liver cirrhosis and six normal subjects were studied to evaluate the effect of %%%iopanoic%%% acid (IA) on thyrotropin secretion. A thyrotropin-releasing-hormone (TRH) test was performed before and 5 days after IA administration (single oral dose of 3 g). After IA administration, a significant increase in TSH response to TRH was observed in normal subjects. In cirrhotics, however, it did not significantly increase after IA administration. The serum T3 and T3/TBG ratio were significantly decreased and the serum T4 and T4/TBG ratio were increased after IA administration in normal subjects and cirrhotics. There was no significant difference in the % decrease in serum T3, % increase in serum T4 or other thyroid hormone parameters including TSH in IA induced TSH responders (R) and non-responders (NR). However, r-T3 before and after IA in R was higher than those in NR. The values for hepatic function tests such as serum %%%albumin%%%, prothrombin time, 45

minutes retention rate of bromsulphalein (BSP45 min) and the cholinesterase (ChE) level in R were not different from those of NR. These results suggested that in cirrhotics, abnormal regulation of the hypothalamo-pituitary system might exist.

9/7/9

07205806 BIOSIS NO.: 198477037717

UPTAKE OF %%%IOPANOIC%%%-ACID AND ITS GLUCURONIDE CONJUGATE BY RAT HEPATOCYTES IN PRIMARY CULTURE

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JOURNAL: Proceedings of the Society for Experimental Biology and Medicine 173 (4): p506-511 1983
ISSN: 0037-9727
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Uptake of %%%iopanoic%%% acid (IOP) and iopanoate glucuronide (IOP-G) was studied in 3-day primary cultures of rat hepatocytes isolated by the collagenase perfusion method. 125I activity of cells after incubation with 125I-IOP (10-100 .mu.M) and 125I-IOP-G (10-100 .mu.M) was used as a measure of uptake. At each concentration, uptake was linear for the first 45 s. In the absence of %%%albumin%%%, the initial uptake velocity was directly proportional to the concentration of IOP or IOP-G and was nonsaturable up to 100 .mu.M. The calculated uptake rate constants for IOP and for IOP-G were 0.059 and 0.048 nmol/(mg protein .cntdot. min .cntdot. .mu.M), respectively. IOP uptake was not inhibited by sodium taurocholate nor by the contrast agents iodipamide, ipodate and iopronic acid. The enhancement of IOP excretion by bile salts noted in vivo evidently does not occur at the uptake step and the hepatic uptake

of both IOP and IOP-G in the absence of %%%albumin%%% is limited by diffusion.

9/7/10
DIALOG(R)File 5:Biosis Previews(R)

07190101 BIOSIS NO.: 198477022012
UPTAKE OF %%%IOPANOIC%%%-ACID BY ISOLATED RAT HEPATOCYTES IN PRIMARY
CULTURE
AUTHOR: BARNHART J L (Reprint); WITT B L; HARDISON W G; BERK R N
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JOURNAL: American Journal of Physiology 244 (6): pG630-G636 1983
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Uptake of %%%iopanoic%%% acid (IOP, an oral cholecystographic contrast agent) was studied in 3 day primary culture of rat hepatocytes isolated by the collagenase perfusion method. 125I activity of cells after incubation with 125I activity of cells after incubation with 125I-IOP (1.0-100 .mu.M) was used as a measure of uptake. At each IOP concentration uptake was linear for the first 45 s. The initial uptake velocity was directly proportional to IOP concentration and was nonsaturable up to 100 .mu.M. The calculated uptake rate constant was 0.67 nmol .cntdot. mg prot-1 min-1 per .mu.M-1. Uptake was only slightly reduce when the incubation was performed at 4.degree. C and was independent of Na concentration. %%%Albumin%%% in the medium reduced IOP uptake. Uptake, however, was always greater than that predicted from the unbound IOP concentration alone. The hepatocyte uptake of IOP apparently occurs by both a passive process and a saturable process. The saturable uptake component depends on an %%%albumin%%%-IOP-hepatocyte interaction. The influence of %%%albumin%%% on uptake occurs possibly by an undefined specific cell surface phenomenon of %%%albumin%%% that promotes uptake of

IOP or by enhancement of the diffusibility of IOP across the unstirred layer.

9/7/11

DIALOG(R)File 5:Biosis Previews(R)

06605250 BIOSIS NO.: 198274021673

COMPETITIVE ACTION OF CONTRAST MEDIA ON URIC-ACID %%%ALBUMIN%%% BINDING

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JOURNAL: Journal of Pharmacological Methods 7 (1): p1-6 1982

ISSN: 0160-5402

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: [An easy method for assessing one of the possible causes of contrast-induced uricosuria in humans, i.e., the capacity of these agents for inhibiting the binding of uric acid to serum %%%albumin%%%, is presented.] This was in vitro study using equilibrium dialysis with bovine serum %%%albumin%%% as the protein substrate. Some compounds used for radiological visualization of the biliary passages apparently compete with uric acid for %%%albumin%%% binding. The meaning and clinical repercussions of this finding are discussed. [Contrast agents examined included iotroxic acid, iodipamide, iodoxamic acid, %%%iopanoic%%% acid, ipodate, iopronic acid, diatrizoic acid, iothalamic acid and iopamidol.].

9/7/12

DIALOG(R)File 5:Biosis Previews(R)

06306490 BIOSIS NO.: 198172040441

COMPETITION BETWEEN SERUM %%%ALBUMIN%%% AND SOLUBLE FRACTION OF LIVER FOR
BINDING OF WARFARIN AND OTHER DRUGS

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JOURNAL: Research Communications in Chemical Pathology and Pharmacology 32 (1): p113-122 1981

ISSN: 0034-5164

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: ENGLISH

ABSTRACT: The binding of warfarin by human serum %%%albumin%%% (HSA) and subcellular fractions from rat liver was investigated to evaluate the roles of such interactions in the pharmacokinetic properties of the anticoagulant. In vitro intracellular distribution studies showed that warfarin was bound primarily by the soluble fraction of rat liver. Equilibrium dialysis studies were carried out to test the hypothesis that the hepatic extraction of warfarin and drug interactions between warfarin and other drugs involved competition between %%%albumin%%% and the soluble fraction of liver. A 3-compartment dialysis cell was designed and constructed for such studies. Three types of competitive binding interactions were identified. %%%lopanoic%%% acid displaced warfarin from HSA, causing increased warfarin in the protein-free compartment and in the compartment containing the soluble fraction. Tolbutamide displaced warfarin from HSA to the liver soluble fraction with relatively little effect on unbound anticoagulant. Sulfinpyrazone produced a 3rd type of interaction characterized by displacement of warfarin from HSA with an increase in the concentration of unbound drug. Competitive binding between %%%albumin%%% and soluble liver proteins is important in the hepatic uptake of warfarin. The 3 compartment dialysis cells may be useful to simulate the distribution of drugs and drug combinations between non-dialyzable macromolecules.

9/7/13

DIALOG(R)File 5:Biosis Previews(R)

06115762 BIOSIS NO.: 198120064729

BINDING OF COUMARIN ANTI COAGULANTS BY SERUM %%%ALBUMIN%%% AND LIVER
FRACTIONS

AUTHOR: WOSILAIT W D (Reprint); RYAN M P; BYINGTON K H

AUTHOR ADDRESS: DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITY
OF MISSOURI, COLUMBIA, MO 65212, USA**USA

JOURNAL: Pharmacologist 22 (3): p246 1980

CONFERENCE/MEETING: MEETING OF THE AMERICAN SOCIETY FOR PHARMACOLOGY AND
EXPERIMENTAL THERAPEUTICS, ROCHESTER, MINN., USA, AUG. 17-21, 1980. PHARMACOLOGIST.

ISSN: 0031-7004

DOCUMENT TYPE: Meeting

RECORD TYPE: Citation

LANGUAGE: ENGLISH

9/7/14

DIALOG(R)File 5:Biosis Previews(R)

05929623 BIOSIS NO.: 198069043610

PHYSIOLOGICAL AND PHARMACOLOGICAL INFLUENCES ON THYROXINE TO 3 5 3' TRI
IODO THYRONINE CONVERSION AND NUCLEAR 3 5 3' TRI IODO THYRONINE BINDING
IN RAT ANTERIOR PITUITARY

AUTHOR: CHERON R G (Reprint); KAPLAN M M; LARSEN P R

AUTHOR ADDRESS: THYROID UNIT, DEP MED, HOWARD HUGHES MED INST LAB, BOSTON,

MASS 02115, USA**USA
JOURNAL: Journal of Clinical Investigation 64 (5): p1402-1414 1979
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Intrapituitary L-thyroxine (T4) to 3,5,3'-triiodo-L-thyronine (T3) conversion with subsequent nuclear binding of T3 is apparently an important pathway by which circulating T4 can inhibit thyrotropin release. The present studies were performed to evaluate various physiological and pharmacological influences on these 2 processes in rat anterior pituitary tissue. Intact pituitary fragments were incubated in buffer-1% bovine serum %%%albumin%%% containing 0.14 ng/ml [131I]T3 and 3.8 ng/ml [125I]T4. Nuclei were isolated after 3 h of incubation and the bound iodothyronines identified by paper chromatography. There was 0.3-1% [125I]T3 contaminating the medium [125I]T4, and this did not change during incubation. Nuclear [125I]T4 was not decreased by 650-fold excesses of medium T3 or T4, suggesting that it was nonspecifically bound. The ratio of nuclear to medium [131I]- and [125I]T3 were expressed as nuclear counts per minute per milligram wet weight of tissue:counts per minute per microliter medium. Intrapituitary T4 to T3 conversion was evidenced by the fact that the nuclear:medium (N:M) ratio for [131I]T3 was 0.45 .+. 0.21, whereas that for [125I]T3 was 2.23 .+. 1.28 (mean .+. SD, n = 51). A ratio (R), the N:M [125I]T3 divided by the N:M [131I]T3, was used as an index of intrapituitary T4 to T3 conversion. Increasing medium T3 concentrations up to 50 ng/ml caused a progressive decrease in the N:M ratio for both T3 isotopes, but no change in the value for R, indicating that both competed for the same limited-capacity nuclear receptors. Increasing concentrations of medium T4 caused no change in the N:M [131I]T3 but did cause a significant decrease in R in 3 of 4 experiments. These results suggest saturation of T4-5'-monodeiodination occurred at lower T4 concentrations than saturation of nuclear T3 binding sites. In hypothyroid rats, the N:M ratios for both [131I]T3 and [125I]T3 were increased ($P < 0.005$), but R was 3-fold higher than in controls ($P < 0.005$). Animals given 10 .mu.g T4/100 g body wt per d [day] for 5 d had significantly decreased N:M

ratios for both [131I]T3 and [125I]T3, as well as a decreased value for R. In fasted rats, neither N:M ratio was depressed, although hepatic T4 to T3 conversion in the same animals was 50% of control ($P < 0.005$). %%%Iopanoic%%% acid (13 .mu.M), but not 6-n-propylthiouracil (29 .mu.M), decreased the N:M [125I]T3 with a significant decrease in the value for R ($P < 0.025$ or less). Neither NaI (6 .mu.M) nor thyrotropin-releasing hormone (7-700 nM) affected the T3 N:M ratios. Intrapituitary T4 to T3 conversion is stimulated in hypothyroidism and depressed in T4-treated animals, whereas opposite changes occur in hepatic T4-5'-monodeiodination. Unlike liver, anterior pituitary T4-5'-monodeiodination is not affected by fasting or incubation with 6-n-propyl-2-thiouracil, but T4 to T3 conversion is inhibited in both by %%%iopanoic%%% acid. There are important differences between anterior pituitary and other tissues in the regulation of T4-5'-monodeiodination.

05841285 BIOSIS NO.: 198019017774
PROPERTIES OF 2 IMPORTANT DRUG BINDING SITES OF HUMAN SERUM %%%ALBUMIN%%%
AUTHOR: FEHSKE K J (Reprint)
AUTHOR ADDRESS: PHARMAKOL INST, UNIV MAINZ, OBERE ZAHLBACHER STR 67, D-6500
MAINZ, W GER**WEST GERMANY
JOURNAL: Naunyn-Schmiedeberg's Archives of Pharmacology 308 (SUPPL): pR24 1979
CONFERENCE/MEETING: DEUTSCHE PHARMAKOLOGISCHE GESELLSCHAFT (GERMAN
PHARMACOLOGICAL SOCIETY) FALL MEETING, MUNICH, WEST GERMANY, SEPT. 3-6,
1979. NAUNYN-SCHMIEDEBERG'S ARCH PHARMACOL.
ISSN: 0028-1298
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation

LANGUAGE: ENGLISH

9/7/16
DIALOG(R)File 5:Biosis Previews(R)

05419418 BIOSIS NO.: 197866005902
THE INTERACTION OF %%%IOPANOIC%%%-ACID AND IOPHENOXIC-ACID WITH HUMAN SERUM
%%%ALBUMIN%%%
AUTHOR: FEHSKE K J (Reprint); MUELLER W E
AUTHOR ADDRESS: PHARMAKOL INST, UNIV MAINZ, OBERE ZAHLBACHER STR 67, D-6500
MAINZ, W GER**WEST GERMANY
JOURNAL: Research Communications in Chemical Pathology and Pharmacology 19 (1): p119-128 1978
ISSN: 0034-5164
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: %%%Iopanoic%%% and iophenoxic acids [biliary contrast agents] are strongly bound to human serum %%%albumin%%%, as revealed from ultracentrifugation experiments. About 2 or 3 high affinity binding sites were found for both drugs. Within the concentration range investigated, %%%iopanoic%%% acid is bound more strongly than iophenoxic acid. The binding to only 1 of the high affinity binding sites produces extrinsic Cotton effects. Further saturation of the high affinity binding sites decreases the extrinsic Cotton effects, possibly due to a binding induced change of the protein conformation.

9/7/17
DIALOG(R)File 5:Biosis Previews(R)

05104617 BIOSIS NO.: 197763025473

THE INTERACTIONS BETWEEN IOPHENOXIC-ACID %%%IOPANOIC%%%-ACID BILIRUBIN AND
HUMAN SERUM %%%ALBUMIN%%% AS STUDIED BY FLUORESCENCE AND SEPHADEX GEL
FILTRATION

AUTHOR: BIRKETT D J; KAPITULNIK J

JOURNAL: Clinica Chimica Acta 71 (2): p129-135 1976
ISSN: 0009-8981
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Unspecified

ABSTRACT: Iophenoxic acid increases the fluorescence of bilirubin bound to human serum %%%albumin%%% at drug/%%%albumin%%% molar ratios lower than 1, while %%%iopanoic%%% acid decreases it. The fluorescence enhancement results probably from a change in the %%%albumin%%%, which in turn causes displacement of bilirubin from the protein. Iophenoxic acid does not affect the high-affinity bilirubin binding site of %%%albumin%%%. Any enhancement in bilirubin fluorescence caused by drug indicates that bilirubin is bound to the low-affinity binding sites of %%%albumin%%%. The use of iophenoxic acid inthe determination of the extent of saturation of the high-affinity bilirubin binding site of %%%albumin%%% may be of value in the clinical management of infants with neonatal jaundice.

9/7/18

04851274 BIOSIS NO.: 197661017413

DRUG DISPLACEMENT OF WARFARIN FROM HUMAN SERUM %%%ALBUMIN%%% A FLUOROMETRIC
ANALYSIS

AUTHOR: HENRY R A; WOSILAIT W D

JOURNAL: Toxicology and Applied Pharmacology 33 (2): p267-275 1975

ISSN: 0041-008X
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: Unspecified

9/7/19
DIALOG(R)File 5:Biosis Previews(R)

04535781 BIOSIS NO.: 197511041924
THE ROLE OF SERUM %%%ALBUMIN%%% IN HEPATIC EXCRETION OF IODIPAMIDE
AUTHOR: SONG C S; BERANBAUM E R
JOURNAL: Investigative Radiology 9 (5): p324 1974
ISSN: 0020-9996
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: Unspecified

9/7/20
DIALOG(R)File 5:Biosis Previews(R)

04399167 BIOSIS NO.: 197457045022
SPECTROSCOPIC TECHNIQUES IN THE STUDY OF PROTEIN BINDING THE USE OF 1
ANILINO-8 NAPHTHALENE SULFONATE AS A FLUORESCENT PROBE FOR THE STUDY OF
THE BINDING OF IOPHENOXIC-ACID AND %%%IOPANOIC%%%-ACID TO HUMAN SERUM
%%%ALBUMIN%%%
AUTHOR: SUDLOW G; BIRKETT D J; WADE D N
JOURNAL: Molecular Pharmacology 9 (5): p649-657 1973
ISSN: 0026-895X
DOCUMENT TYPE: Article

RECORD TYPE: Citation
LANGUAGE: Unspecified

9/7/21
DIALOG(R)File 5:Biosis Previews(R)

04269501 BIOSIS NO.: 197410015656
PROTEIN BINDING AND DRUG INTERACTIONS
AUTHOR: SUDLOW G; BIRKETT D J; WADE D N
JOURNAL: Australian and New Zealand Journal of Medicine 3 (3): p336-337
1973
ISSN: 0004-8291
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: Unspecified

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10/3/1
DIALOG(R)File 5:Biosis Previews(R)

07205806 BIOSIS NO.: 198477037717
UPTAKE OF %%%IOPANOIC%%%-ACID AND ITS GLUCURONIDE
%%%CONJUGATE%%% BY RAT
HEPATOCYTES IN PRIMARY CULTURE
AUTHOR: BARNHART J L (Reprint); WITT B L
AUTHOR ADDRESS: DEP RADIOL, UNIV CALIF SAN DIEGO, LA JOLLA, CALIF 92093,
USA**USA
JOURNAL: Proceedings of the Society for Experimental Biology and Medicine
173 (4): p506-511 1983
ISSN: 0037-9727
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

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11/3/1
DIALOG(R)File 5:Biosis Previews(R)

17214523 BIOSIS NO.: 200300173242
Convective distribution of macromolecules in the primate brain demonstrated using computerized tomography and magnetic resonance imaging.
AUTHOR: Nguyen Tung T; Pannu Yashdip S; Sung Cynthia; Dedrick Robert L; Walbridge Stuart; Brechbiel Martin W; Garmestani Kayhan; Beitzel Markus; Yordanov Alexander T; Oldfield Edward H (Reprint)
AUTHOR ADDRESS: Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke, National Institutes of Health, 10 Center Drive, Building 10 Room 5D37, MSC 1414, Bethesda, MD, 20892-1414, USA**USA
AUTHOR E-MAIL ADDRESS: OldfielE@ninds.nih.gov
JOURNAL: Journal of Neurosurgery 98 (3): p584-590 March 2003 2003
MEDIUM: print
ISSN: 0022-3085
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

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